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ANTTI JOUKAINEN

New Bioabsorbable Implants for the Fixation of Metaphyseal Bone

An Experimental and Clinical Study

Doctoral dissertation

To be presented by permission of the Faculty of Medicine of the University of Kuopio
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Department of Orthopaedics, Traumatology and Hand Surgery
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ABSTRACT

The purpose of the present study was to investigate the suitability of bioabsorbable drawn self-reinforced polyglycolide (SR-PGA) and poly-L/DL-lactide 70:30 (SR-PLA70) implants in experimental and clinical fixations of cancellous bone osteotomies, arthrodeses and fractures.

The study consists of a set of two experimental and two clinical studies, including 109 experimental animals and 87 patients, respectively.

In the experimental studies, the right femora of 77 Wistar rats were osteotomized and fixed with either drawn SR-PGA or SR-PLA70 bioabsorbable pins. Both femora of each rat were taken as specimens at follow up times ranging from 1 to 52 weeks after the operations. Radiological, histological, histomorphometrical, microradiographic, and oxytetracycline-fluorescence studies were performed. In the mechanical studies, four pins of SR-PLA70 or SR-PGA were implanted in the dorsal subcutaneous tissue of 32 rats for mechanical testing at 1 – 52 weeks.

The clinical studies were prospective randomized studies concerning osteosynthesis with either SR-PLA70 or self-reinforced poly-L-lactide (SR-PLLA) screws. In the third study, 62 ankle fractures were treated using bioabsorbable screws in the fixation. The patients were followed for one year using clinical examination, radiography and Olerud-Molander score. The second clinical study included 25 patients with 32 painful feet with hallux valgus needing proximal osteotomy or arthrodeses of the 1st tarsometatarsal (TMT) joint. The patients were followed up for one year using radiography, clinical examination and hallux-metatarso-interphalangeal scoring (HMIS).

The initial flexural strengths of the SR-PGA and SR-PLA70 pins were 270 ± 30 MPa and 214 ± 4.2 MPa, respectively. The initial flexural modulus of the SR-PGA and SR-PLA 70 pins were 13 ± 2 GPa and 6.0 ± 0.5 GPa, respectively. At 3 weeks in vivo, the SR-PGA pins had maintained 50 % of flexural strength and 46 % of modulus of the initial value, whereas SR-PLA70 pins retained 43 % of their flexural strength and 41 % of their modulus compared to the initial value at one year after implantation.

In the ankle fractures patients, the SR-PLA70 and SR-PLLA study groups differed significantly only in the mean time of sick leave (SR-PLA70 60 days, SR-PLLA 65 days, p=0,02). At the one year follow-up, syndesmotic ossification was more common in the SR-PLA70 group (5 vs. 1 patient, p=ns.). There were no infections or signs of tissue reactions in either of the study groups.

In the hallux valgus patients, 26 of 32 feet were treated with proximal osteotomy of the 1st metatarsal bone, and the other 6 feet with concomitant laxity of the 1st tarsometatarsal (TMT) joint were treated with arthrodesis. At 12 weeks, bony union in 31 out of 32 osteotomies or arthrodeses was seen. At one year, the change of hallux valgus angle was 16° and 16°, and the change of intermetatarsal angle was 8° and 9° in SR-PLA70- and SR-PLLA-groups, respectively. HMIS-scores were 90 and 92 accordingly. No signs of tissue reaction were seen during the follow-up time which lasted up to one year. Radiologically, the screw channel had not disappeared in any of the patients in the clinical studies by the one year follow-up.

The present investigation showed that the mechanical strength and fixation properties of SR-PGA and SR-PLA70 pins are suitable for fixation of cancellous bone osteotomies in rats. Bioabsorbable SR-PLA70- and SR-PLLA-screws are suitable in the fixation of ankle fractures, the proximal osteotomy of the 1st metatarsal bone, and TMT joint arthrodesis in the treatment of hallux valgus deformity.

National Library of Medicine Classification: QU 98, QY 60.R6, WE 190, WE 880, WE 883
Medical Subject Headings: Absorbable Implants; Ankle Injuries; Bone Screws; Bone Substitutes; Femur; Follow-Up Studies; Fracture Fixation, Internal; Fractures, Bone; Hallux Valgus; Humans; Lactic Acid/analogs & derivatives; Materials Testing; Osteogenesis; Osteotomy; Rats, Wistar; Time Factors; Treatment Outcome

To Sarukka, Elli and Eetu

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This work was carried out at the Department of Orthopaedics, Traumatology and Hand Surgery of Kuopio University Hospital, the Department of Orthopaedics and Traumatology of Helsinki University Hospital, the Department of Surgery of Iisalmi District Hospital and the Department of Surgery of Mikkeli Central Hospital, between the years 1997 and 2008.

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Kuopio, May 2008

Antti Joukainen

ABBREVIATIONS

ºC	degrees Celsius
GPa	GigaPascal (10^9 N/m^2)
HMIS	hallux-metatarso-interphalangeal score
HV	hallux valgus
IMA	intermetatarsal angle
kg	kilogram
MPa	MegaPascal (10^6 N/m^2)
MT	metatarsal
MTP	metatarsophalangeal
MTPJ	metatarsophlangeal joint
MW	molecular weight
ns.	not significant
OTC	oxytetracycline
PGA	polyglycolid acid or polyglycolide
PDLA	poly-dextro-lactic acid or poly-D-lactide
PLA	polylactic acid or polylactide
PLLA	poly-levo-lactic acid or poly-L-lactide
PLA70	poly-L/DL-lactide 70:30
ROM	range of motion
SR-PGA	self-reinforced polyglycolic acid
SR-PLLA	self-reinforced poly-L-lactic acid
SD	standard deviation
SR	self-reinforced
T_g	glass transition temperature
TMT	tarsometatarsal
TMTJ	tarsometatarsal joint

LIST OF ORIGINAL PUBLICATIONS

The present study is based on the following papers, referred to in the text by their Roman numerals:

I. Joukainen A, Pihlajamäki H, Mäkelä EA, Ashammakhi N, Viljanen J, Pätiälä H, Kellomäki M, Törmälä P, Rokkanen P: Strength retention of self-reinforced drawn poly-L/DL-lactide 70/30 (SR-PLA70) rods and fixation properties of distal femoral osteotomies with these rods. An experimental study on rats. J Biomater Sci Polym Ed 11: 1411-28, 2000

II. Pihlajamäki H, Mäkelä EA, Ashammakhi N, Viljanen J, Pätiälä H, Rokkanen P, Pohjonen T, Törmälä P, Joukainen A. Strength retention of drawn self-reinforced polyglycolide rods and fixation properties of the distal femoral osteotomies with these rods. An experimental study on rats. J Mater Sci Mater Med 13: 389-95, 2002

III. Joukainen A, Partio EK, Waris P, Joukainen J, Kröger H, Törmälä P, Rokkanen P: Bioabsorbable screw fixation for the treatment of ankle fractures. J Orthop Sci 12: 28-34, 2007

IV. Joukainen A, Partio E, Mäkelä E A, Törmälä P, Rokkanen P: Bioabsorbable SR-PLA70 and SR-PLLA screws in 32 proximal hallux valgus corrections in 25 patients. J Bone Joint Surg-Br, submitted

CONTENTS

1. INTRODUCTION

Osteosynthesis is the process which restores the stuctural integrity of a fractured or osteotomized bone during bone healing. The ideal implant in osteosynthesis will be adequate in strength, will not disturb the normal healing and will biodegrade after bony union with no need for secondary implant removal operation. Different metallic alloys, usually steel, fulfill the first two demands, but in spite of their good biocompatilibility, their major problem is that fixation is too rigid, causing the development of stress-protection atrophy due to the difference in the modulus of elasticity (Young's modulus) between cortical bone (E = 10-30 GPa) and the metals (E = 100-200 GPa): the stiffer the bone plate, the higher bone loss and correspondingly the greater loss of mechanical properties occurring (Claes 1989, Paavolainen et al. 1978, Perren 2002, Rosson and Shearer 1991, Uhthoff et al. 2006). Another disadvantage of metallic implants is that the osteosynthesis material may have to be removed in a second operation (Ambrose and Clanton 2004, Brown et al. 1993).

After the invention of fully bioabsorbable implants, ideal osteosynthesis seemed to be achievable. However, though the bioabsorbable bone fixation devices became available about 40 years ago (Kulkarni et al. 1966, Kulkarni et al. 1971, Schmitt and Polistina 1969), the suboptimal strength values of the initial implants meant that further development of the materials was necessary (Vert et al. 1984). In 1987, after the introduction of the self-reinforcing (SR) technique used to reinforce the implant with oriented, fibrous elements made of the same material as the matrix (Törmälä et al. 1987, Törmälä et al. 1988), adequate strength values of polyglycolide (PGA) and polylactide (PLA) implants were achieved allowing fixation of bone fractures and osteotomies.

Theoretically, bioabsorbable implants possess several of the properties of an ideal osteosynthesis device: the strength is adequate to let the fracture or osteotomy heal, their elasticity is near to that of bone, fixation strength decreases gradually, the implant itself disappears through normal metabolic pathways without causing harmful effects and there is no need for implant removal operation.

In 1984, the first ankle fractures were fixed using polyglycolide/polylactide copolymer rods (Rokkanen et al. 1985). Since then, several materials have been studied in order to develop an optimal synthetic, bioabsorbable osteosynthesis implant useful for the internal fixation of fractures and osteotomies (Claes et al. 1996, Majola et al. 1991, Päivärinta et al. 1993, Saikku-Bäckström et al. 1999, Törmälä et al. 1987, Törmälä et al. 1991, Vert et al. 1992). The use of different bioabsorbable materials in orthopaedics and traumatology is now widely accepted and bioabsorbable implants have been used worldwide in experimental and clinical studies (Ambrose and Clanton 2004, Pihlajamäki et al. 1998, Rokkanen 2001).

SR-PGA and SR-PLLA implants possess the strength of cortical bone, which is proposed to be the safe strength level for an implant to be useful in bone fixation (Törmälä et al. 1998). However, SR-PGA implants manufactured with the sintering technique totally lose their strength rapidly in 4-8 weeks (Törmälä et al. 1991, Vainionpää et al. 1987), whereas SR-PLLA strength retention is unnecessarily long, lasting over 36 weeks (Jukkala-Partio et al. 2001, Manninen and Pohjonen 1993) and much longer than the healing of metaphyseal bone. Healing of osteotomy or fracture in metaphyseal bone occurs in 6-12 weeks (Aro and Rokkanen 1995), and the optimal strength retention time of a bioabsorbable implant would be close to this time.

The bioabsorbance time of PLA is dependent on the proportions of stereoisomers, namely D- and L-monomers, in the polymer chain (Kulkarni et al. 1971). Pure PLLA is highly crystalline and may exist or be only partly degraded at times of five to nine years or even longer in the operated area (Bergsma et al. 1995a, Jukkala-Partio et al. 2002, Voutilainen et al. 2002). D-monomers of PLA have reduced the crystallinity and this decreases time needed for biodegradation though it also diminishes the strength of the material. A racemic polymer of polylactic acid, poly-DL-lactide (PDLLA), is totally amorphous and degrades much faster than PLLA (Kulkarni et al. 1971). Further, the copolymers of L-lactide and DL-lactide have been shown to have shorter biodegradation times than PLLA, with the rate depending on the monomer ratios (Andriano et al. 1994, Gogolewski 2000, Majola et al. 1991, Vert et al. 1984). SR-PLA70 copolymers manufactured with a self-reinforcing technique were developed in 1996 and these materials have similar initial strength and strength retention *in vitro* as the SR-PLLA material (Pohjonen and Törmälä 1996). This

stereocopolymer material with an initially amorphous crystalline morphology also degrades faster than SR-PLLA, which might be a benefit in fracture or osteotomy healing in two ways: shorter strength retention of the implant loads bone earlier concluding to more vigorous new bone formation and bone healing; and faster degradation of the implant may provoke earlier ingrowth of bone into the implant channel and normal bone architecture. Possible theoretical disadvantages of shorter degradation time are inadequate strength retention concluding fracture or osteotomy dislocation, and harmful tissue reactions.

The self-reinforcing technique also affects the degradation time of the bioabsorbable implant. Non-reinforced PGA implants lose their initial strength totally in four weeks, whereas the bending strength of self-reinforced PGA manufactured with the sintering technique was still 10-20 MPa at four weeks (Törmälä et al. 1987). The die-drawing technique has been proven to be most efficient way to produce self-reinforced implants (Pohjonen et al. 1993), but it has not been applied manufacturing SR-PGA implants.

In experimental studies, SR-PGA and SR-PLLA have shown good biocompatibility (Majola et al. 1991, Nordström et al. 2001, Santavirta et al. 1990, Törmälä et al. 1991), but in the clinical studies, rapidly bioabsorbable SR-PGA implants were found to evoke an adverse tissue reaction in 5 % of patients at 11 weeks, on average (Böstman and Pihlajamäki 2000b). Slowly biodegradable SR-PLLA implants may occasionally cause tissue reactions at times as late as nine years after the initial operation (Böstman and Pihlajamäki 2000b, Voutilainen et al. 2002). Novel implant materials need to be carefully tested before clinical use (Lubowitz and Poehling 2008).

The high crystallinity of PLLA is probably one of the factors that makes PLLA particles resistant to hydrolysis and biodegradation. During the degradation, even more crystalline polymer residues form, and these are considered to cause the late foreign body reactions (Bergsma et al. 1995a). Theoretically, initially amorphous SR-PLA70 would be an appropriate material in orthopaedic implants as a way of avoiding these harmful effects (Ambrose and Clanton 2004).

The purpose of the present study was to evaluate experimentally the biomechanical properties and histological effects of drawn SR-PGA and SR-PLA70 implants in the distal femur of a rat, and clinically SR-PLLA and SR-PLA70 screws in osteotomy and fracture

osteosynthesis of metaphyseal bone. Ankle fracture and hallux valgus disease were chosen as indications for the clinical studies, because these conditions need a metaphyseal bone area stabilization in the operative technique, they are common and suitable for collecting patients in the study cohorts, and, with thin subcutis of the operative regions, they were considered to benefit of no need for ostesynthesis removal operations. Removal rate for metallic implants above 19–54 % (depending on the fracture type) would make resorbable implants cost-effective (Böstman 1996). It is essential to know which bioabsorbable material is suitable for implants to be used in osteosynthesis, because the most important disadvantage of bioabsorbable implants, the foreign body reaction, is essential to avoid (Ambrose and Clanton 2004, Lubowitz and Poehling 2008). If the novel SR-PGA implant works well in bone fixation in an experimental study, it can be applied in clinical studies. If SR-PLA70 implants prove to be efficient and safe for the fixation of osteotomies and fractures, this is a clear benefit since this bioabsorbable material has a medium bioabsorbance time, which is especially useful in certain orthopaedic implants.

2. REVIEW OF THE LITERATURE

Poly-alpha-hydroxy acids constitute a class of polymers which are derived from alpha-hydroxy acids. Polyglycolide and polylactide are the strongest polymers of this class and they have been investigated for over 40 years (Kulkarni et al. 1966, Schmitt and Polistina 1969, Kulkarni et al. 1971, Vert et al. 1981). Bioabsorbable polyester devices have been used experimentally in bone fixation since 1971 (Cutright et al. 1971) and clinically since 1974 (Roed-Petersen 1974).

The self-reinforcing technique (SR) was introduced by Törmälä (Törmälä et al. 1988, Törmälä et al. 1991). This technique enabled the manufacturing of bioabsorbable implants with sufficient strength to permit their use in bone fixation. In this method, fibres of polyester are sintered together at a high temperature and pressure creating an implant in which the matrix and reinforcing fibres are of the same material. Ultra-high-strength (bending strength up to 405 MPa) SR-PGA rods were developed using the fibrillation die-drawn SR-technique. The strength of these rods is still much higher than that of absorbable implants manufactured by any other method (Table 1) (Törmälä 1992, Törmälä 1998, Gunja and Athanasiou 2006). Thus, the molded implants are suitable in orthopaedics and traumatology only for indications where the implant is not loaded with high bending forces, for example in ACL-reconstructions.

Table 1. Mechanical properties of different polyesters, bone and steel

Material	Bending strength (MPa)	Shear strength (MPa)	Elastic modulus (Gpa)	Strength ret.	Reference
PGA	218	95	7		Pohjonen et al. 1989
SR-PGA	330 - 415	260	13 - 18		Pohjonen et al.1989, Törmälä 1992
PLLA	40 - 140		5 - 10	40%/8wk	Gogolewski 2000, Törmälä et al. 1998
SR-PLLA	245 - 300	136 - 156	8,2 - 10		Manninen and Pohjonen 1993, Törmälä 1992, Pohjonen and Törmälä 1996
PDLA	200		9		Weiler et al. 1996, Gogolewski and Mainil-Varlet 1996
P(L/DL)LA70	155 - 163			36 wk, 40%/12wk	Claes et al. 1996, Gogolewski 2000
SR-P(L/DL)LA70	163 - 170	110 - 116	5 - 6		Pohjonen and Törmälä 1997b, Pohjonen et al. 1997
SR-PLA96	228 - 274	140 - 152	5,4 - 8,4	24 wk	Saikku-Bäckström 2005
Cortical bone	180-195	68 - 100	9,5 - 11		Reilly and Burstein 1975, Tonino et al. 1976
Cancellous bone	2,6 - 7,6	10			Stone et al. 1983, Kaplan et al. 1985
Bone	100-200	68	7 - 40		Gogolewski 2000
Stainless steel	400		190		Claes 1989

Table 2. Factors affecting the degradation of biodegradable polymers (Vert et al. 1992)

Chemical structure
Chemical composition
Distribution of repeat units in multimers
Presence of ionic groups
Presence of unexpected units or chain defects
Configurational structure
Molecular weight
Molecular weight distribution (polydispersity)
Presence of low molecular weight compounds (monomer, oligomers, solvents, iniators, drugs, etc.)
Processing conditions
Shape
Sterilizing process
Morphology (amorphous vs. semicrystalline, presence of microstructures, presence of residual stresses)
Annealing
Storage history
Site of implantation
Adsorbed and absorbed compounds (water, lipids, ions, etc.)
Physiochemical factors (shape and size changes, variations of diffusion coefficients, mechanical stresses, stress and solvent-induced cracks, etc.)
Mechanism of hydrolysis (enzymatic vs. aqueous)

2.1. POLYGLYCOLIC ACID

Bischoff and Walden synthesized low molecular weight polyglycolic acid (PGA) already in 1893. High molecular weight PGA with plastic properties capable of being melt-extruded into strong, self-supporting fibers and films was introduced by Higgins in 1954 and PGA was the first bioabsorbable suture material (Higgins 1954). PGA has been commercially available as a suture material since 1970 (Gilding and Reed 1979).

2.1.1. Chemical properties

PGA with a high molecular weight is a hard, tough, crystalline polymer, melting at approximately 224-228 °C with a glass transition temperature (T_g) of 36 °C (Engelberg and Kohn 1991, Frazza and Schmitt 1971, Törmälä et al. 1998). PGA is insoluble in most of the common polymer solvents. The molecular weight of a polymer to allow it to be spun into a fibre form should be 20 000 - 145 000 (Frazza and Schmitt 1971). PGA can also be processed into different kinds of objects like films, pins, rods, plates and screws (Gilding and Reed 1979, Schmitt and Polistina 1969, Törmälä et al. 1988).

PGA can be synthesized from glycolide under the influence of an inorganic metal salt catalyst at a low concentration by ring opening polymerization (Schmitt and Polistina 1969):

$(CH_2CO - O - CH_2CO - O)_n -$

Polyglycolic acid (PGA) or polyglycolide

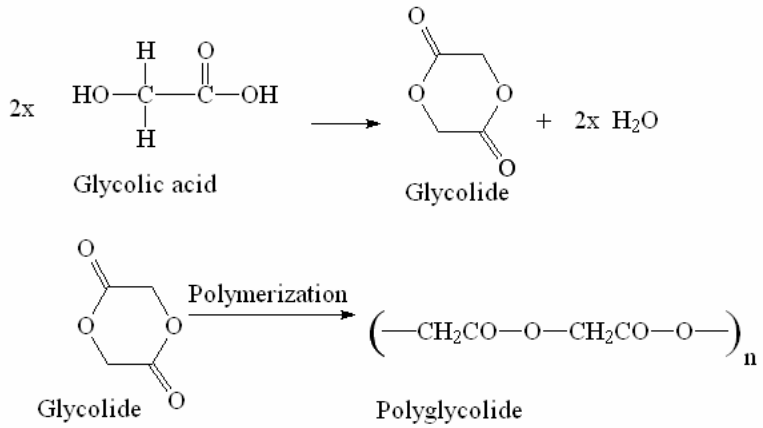


Figure 1. Synthesis of polyglycolide

2.1.2. Biodegradation

The biodegradation of polyesters like PGA and PLA occurs mainly through nonspecific hydrolytic scission (Hollinger and Battistone 1986) by essentially the same mechanism in

vivo and in vitro. The enzymatic activity of non-specific esterases and carboxyl peptidases may hasten the degradation process in vivo (Williams 1982): PGA is broken down into glycolic acid monomers which are converted enzymatically into glycine which can be used in protein synthesis or metabolized to pyruvate which can be used in mitochondrial energy production. The final products of degradation are mainly carbon dioxide and water, though glycolic acid is also excreted in urine (Frazza and Schmitt 1971, Hollinger and Battistone 1986, Williams 1982).

Biodegradation of polyesters generally occurs in two phases. In the first phase, the polymer chains are broken down through hydrolysis. In this phase, the molecular weight decreases first, followed by mechanical strength loss, and in the end by a loss of mass (Hollinger and Battistone 1986). In the second phase, the implant loses its form and breaks physically into particles, which are phagocytosed by macrophages, and the byproducts are excreted by the kidneys and lungs. The corresponding biological response to the degrading polymer is thought to happen as a result of either a build up of acidic degradation products or due to a response to the particulates of the polymer. Buffer substances released from the surrounding tissue may avoid the acidification of tissue adjacent to the degrading implant (Partio 1992).

The degradation time varies depending on tissue environment, the molecular weight, the purity and crystallinity of the PGA, as well as on the size and shape of the implant (Table 2). A large size of the implant and a high molecular weight will delay the degradation time (Hollinger and Battistone 1986, Törmälä et al. 1991, Vert et al.1994).

The degradation time was found to be shorter in bone than in subcutaneous tissue (Vasenius et al. 1990). PGA implants degraded from periphery towards the center in cancellous bone and partly in cortical bone of rabbits within 12 weeks (Vainionpää 1986). The degradation of PGA cylinders in the sheep femora occurred in 20 weeks (Christel et al. 1982), whereas 4,5 mm PGA screws in the rabbit distal femora disappeared within 36 weeks (Böstman et al. 1992b). PGA did not degrade totally within nine months when PGA cylinders were implanted in the tibial cortices (Vert et al. 1984), or osteotomized distal femora (Nordström et al. 2001) of rats.

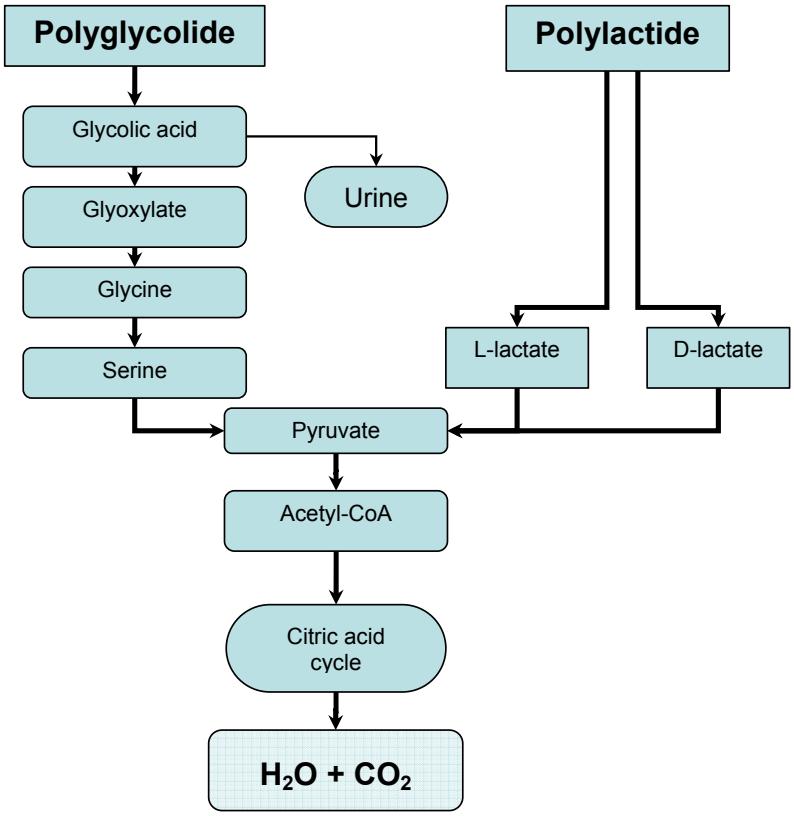


Figure 2. Biodegradation of polyglycolide and polylactide.

2.1.3. Biocompatibility

In vitro, PGA proved to be an immunologically relatively inert, causing only slight lymphocyte but not phagocyte activation (Santavirta et al. 1990). Experimentally, the foreign-body reactions with PGA implants in metaphyseal bone have occurred most vigorously between three and 12 weeks after implantation. In the first phase, giant cells adhere to the implant in the first three to six weeks (Päivärinta et al. 1993), after which macrophages and polymorphonuclear leukocytes dominate at 12 weeks (Böstman et al. 1992b).

In the clinical studies, polyglycolide materials have provoked an adverse tissue response that exhibits the characteristics of an inflammatory, abacterial foreign-body reaction. Adverse tissue responses to polyglycolide implants have been reported in several reports,

with the incidence varying from 2.0 to 46.7% (Böstman and Pihlajamäki 2000b).The highest incidence has been observed in fractures of the distal radius and the scaphoid bone (Casteleyn et al. 1992, Hoffmann et al. 1992, Pelto-Vasenius et al. 1995). In the largest series published, an adverse tissue reaction occurred in 5.3 % (107 reactions) of operations using SR-PGA implants (Böstman and Pihlajamäki 2000a). However, the frequency of foreign-body reactions significantly decreased when the dye was omitted from the PGA implant material (Böstman and Pihlajamäki 2000a, Partio 1992). The risk of adverse tissue reactions has hindered the use of polyglycolide implants in favour of bioabsorbable implants which have slower rates of degradation, like PLA.

2.1.4. Mechanical properties

It has been proposed that the strength of an implant should exceed the strength of cortical bone to achieve a safe fracture fixation (Törmälä et al.1998). The first PGA implants were produced by extrusion or injection melt moulding techniques (Vert et al. 1981), which resulted in bioabsorbable polymers with strength values typically over 200 MPa and thus were useful for bone fixation (Table 1).

With the self-reinforcing manufacturing technique, the initial bending strength of SR-PGA screws and rods may rise up to 405 MPa and the shear strength up to 250 MPa (Törmälä et al. 1991). The strength of PGA is superior to PLA, but SR-PGA implants lose their strength rapidly within four to eight weeks (Vasenius et al. 1990). The physical properties of these implants have been described in many experimental (Miettinen et al. 1992, Nordström et al. 2002, Vainionpää et al. 1986, Weiler et al. 1996) and clinical studies (Böstman et al. 1989, Casteleyn et al. 1992, Kankare et al. 1996, Mäkelä et al. 1992, Partio et al. 1992a, Rokkanen et al. 1985, Kankare 1997, Kankare and Rokkanen 1998).

2.2. POLYLACTIDE

2.2.1. Chemical properties

Monomeric lactic acid belongs to the group of alpha-hydroxy acids; lactide is its cyclic diester form. Lactic acid molecule is an asymmetric compound including a chimeric carbon atom. Thus, cyclic lactide includes two chimeric carbon atoms. Lactide has two enantiomeric forms, L and D, with opposite configurational structures but similar intrinsic chemical properties and exists as 4 diastereoisomers: L-lactide, D-lactide, DL-isomer (meso-lactide), and DL-lactide (racemic lactide) (Vert et al. 1984) (Figure 4).

Both L- and D-monomers of lactide exist in human serum. All cells, especially muscle, produce L-lactic acid as a product of glycolysis in a balanced equilibrium during an inadequate oxygen supply (Poeze et al. 2003). The level of D-lactic acid in human blood (Brandt 1982) is normally low, originating from dietary intake and from colonic bacterial fermentation. D-lactate serum level is increased in septic shock patients because of their poor splanchnic circulation (Poeze et al. 2003).

A high-molecular-weight polylactic acid (PLA) with thermoplastic properties was noticed to be a hard, pale-coloured, semi-crystalline polymer (Schneider 1955).

Unlike polyglycolic acid, polylactic acid is hydrophobic due to the presence of its methyl group. This makes the compound more resistant to polymer chain cleaving water molecules (hydrolysis), and explains the slower degradation compared to polyglycolic acid (Hollinger and Battistone 1986). Another factor explaining the slower biodegradation of poly-L-lactic acid is its crystallinity. Poly-L-lactic acid with a molecular weight over 100 000 is highly crystalline (Törmälä et al. 1998, Vert et al. 1981), but poly-D-lactic acid and co-polymers containing more than 85 % of D-monomers are intrinsically amorphous (Andriano et al. 1994, Vert et al. 1984).

2.2.2. Synthesis of polylactide

Initially, poly-alpha-hydroxyacids like PLA were synthesized by simple step-growth polymerization, but the resulting polymers had low molecular weights and poor mechanical properties (Vert et al. 1984). Long-chain, high-molecular weight PLA is produced most efficiently by ring opening polymerization of cyclic diesters of lactic acid (Hyon et al. 1997, Lowe 1954) under the influence of a catalyzing inorganic metal salt (antimony, zinc, lead, or tin catalyst) present at a low concentration (Vert et al. 1984). The resultant polymer is commonly described with the formula:

$\{CH(CH_3)CO - O - CH(CH_3)CO - O\}_n$ -

Polylactic acid (PLA) or polylactide

Melt-spun fibres of polylactide can be produced with a MW between 180 000 and 260 000 Daltons, while solution-spun fibres can be produced with a MW between 350 000 and 530 000 Daltons (Gogolewski and Pennings 1983).

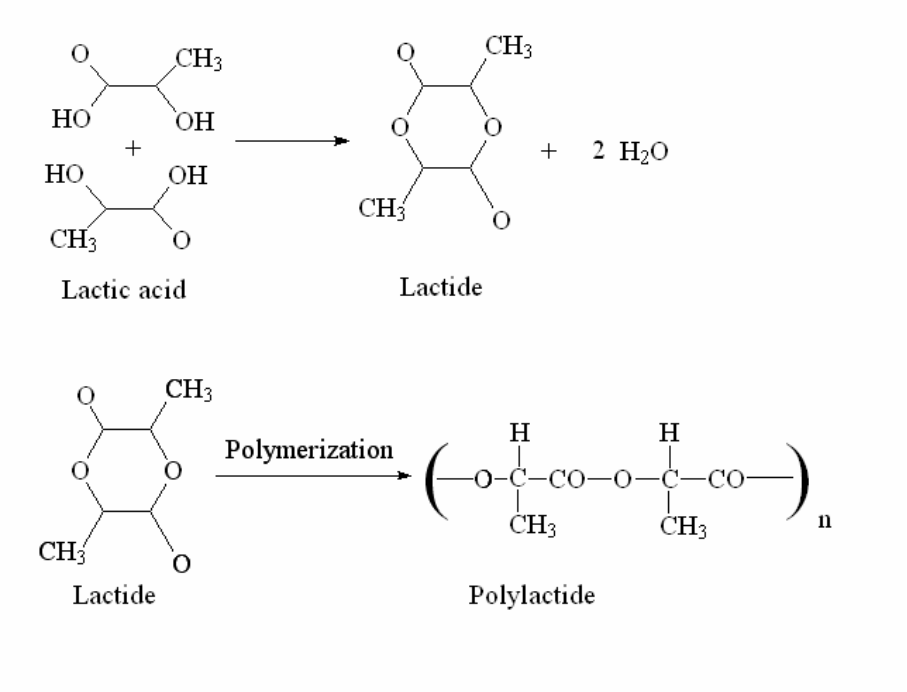


Figure 3. Synthesis of polylactide

2.2.3. Biodegradation of polylactide

The first stage of the degradation process of PLA is non-enzymatic random hydrolytic cleavage of ester linkage decreasing the molecular weight (Pitt et al. 1981). Weight loss cannot be seen before the MW decreases to 15,000 or less. The rate of chain scission increases after the commencement of weight loss (Pitt et al. 1981).

Polylactide chains are mainly cleaved by hydrolytic scission to form monomeric L- and D-lactic acids. L-lactic acid is oxidized by L-lactate dehydrogenase to pyruvate whereas D-lactate is metabolized more slowly by D-2-hydroxy-acid-dehydrogenase to pyruvate. Pyruvate is eliminated from the body through the citric acid cycle, primarily as carbon

dioxide and water (Gogolewski 2000, Hollinger and Battistone 1986) and with small amounts being present in the urine and faeces (Brady et al. 1973).

The rate of degradation of the PLA chain is dependent on several factors, for example stereoisomeric proportions of different isomers of lactide (Kulkarni et al. 1971), crystallinity (Bergsma et al. 1995a, Hollinger 1983, Niiranen et al. 2004, Vert et al. 1992), molecular weight (Gogolewski et al. 1993, Pitt et al. 1981), polydispersity (Gogolewski and Mainil-Varlet 1997), the load acting on the implant, the size and shape of the implant (Gogolewski 2000), methods of processing the implant (Törmälä et al. 1998), and sterilization (Gogolewski and Mainil-Varlet 1996, Gogolewski and Mainil-Varlet 1997, Nuutinen et al. 2002). A slight difference is observed in the rate of degradation in different body sites (Vasenius et al. 1990), but the degradation has been observed to proceed in vivo faster than in vitro (Pohjonen et al. 1997).

PLLA with a molecular weight over 100 000 is inherently a crystalline polymer (Vert et al. 1984) making it more resistent to water molecules and leading to a very long (up to ten years) final degradation time (Voutilainen et al. 2002). Additionally, there are reports of foreign body reactions after the use of as-polymerized PLLA, which during the biodegradation produces highly crystalline, very slowly degrading particles (Bergsma et al. 1995b). When the degradation of highly crystalline poly-L-lactide was compared to less crystalline poly-DL-lactide, the latter showed a faster rate of degradation (Kulkarni et al. 1971), and it has been shown that by changing the proportions between the monomeric units constituting the polymer chain, it is possible to modify the implant crystallinity and thus biodegrading time (Bergsma et al. 1995a, Bergsma et al. 1995b, Christel et al. 1982, Gogolewski 2000, Vert et al. 1984). However, also initially amorphous PLA does crystallize to some extent as the degradation proceeds (Pohjonen and Törmälä 1996). Additionally, increasing the D-monomer component of the PLA reduces the mechanical strength, and amorphous poly-DL-lactide used in some experimental studies have been considered as being inadequate in osteosynthesis (Engelberg and Kohn 1991, Vert et al. 1984).

The presence of certain enzymes has also been shown to hasten the degradation of PLA in vitro. Non-hydrolytic pronase, proteinase K, and bromelain significantly, and ficin, esterase, and trypsin with a smaller response increased the hydrolysis rate of PLA in vitro; lactate dehydrogenase had no effect (Williams 1982). The enzymatic degradation process

has been suggested to be more extensive at the later stage of the partially hydrolyzed polymer (Gogolewski et al. 1993).

The final degradation time of PLA varies. In an experimental study, a 6.3 mm SR-PLLA screw had been replaced by dense bone tissue 7.3 years after implantation in sheep proximal femur (Jukkala-Partio et al. 2002), and in a long-term clinical study, intracellular polylactide particles could still be found extraosseously near the screw channel 9.6 years after the initial operation, and the implant channel was found to be filled with loose soft tissue, not bone (Voutilainen et al. 2002).

The less crystalline stereo-copolymers of L-lactide with D- or DL-lactide have faster degradation rates than 100 % pure PLLA (Kulkarni et al. 1971), with the rate depending on the monomer ratios (Bergsma et al. 1995b, Vert et al. 1984). It was observed from mass-loss studies of PLA and PLA96 that incorporation of 4 % D-lactide could enhance the degradation rate by a factor of two (Bergsma et al. 1995c). Complete degradation of amorphous SR-PLA (70/30) is believed to take 2-3 years, as extrapolated from in vitro hydrolysis studies (Pohjonen and Törmälä 1996).
In another study, non-reinforced P(L/DL)LA70:30 pins were used in the fixation of femoral condyle osteotomy of sheep. At 36 months, the pins had microscopically disappeared and the channels were filled with bone or scar tissue (Prokop et al. 2005a).

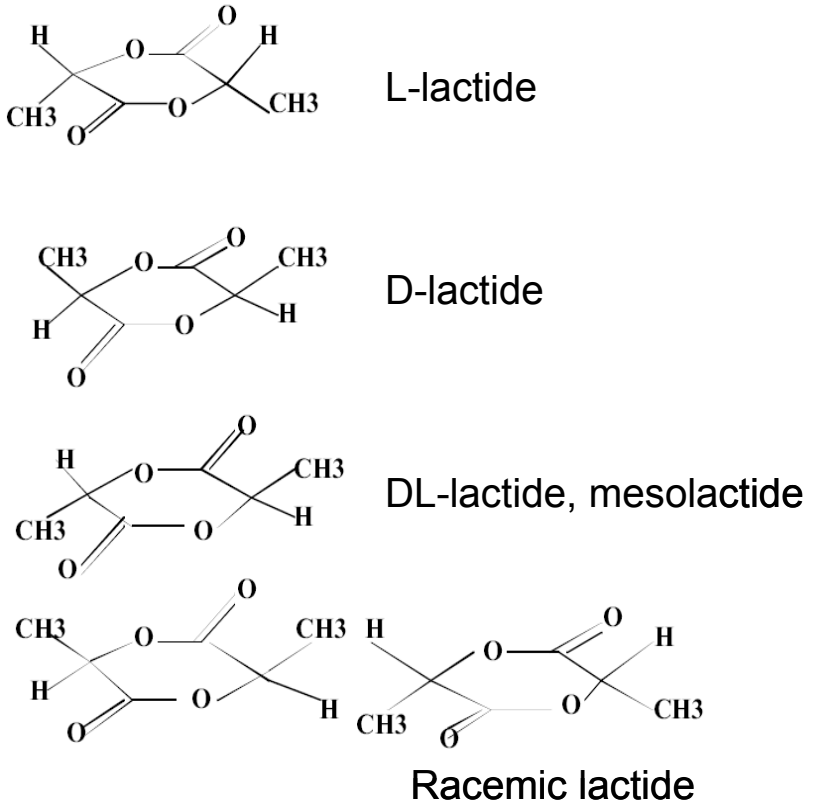


Figure 4. Stereoisomers of lactide. (Vert 1984)

2.2.4. Biocompatibility of polylactide

In experimental studies, the biocompatibility of PLA has been well tolerated by the host tissue (Cutright and Hunsuck 1972, Majola et al. 1991, Matsusue et al. 1995, Nordström et al. 2001). PDLLA and PLLA were well-tolerated and the tissue response inside muscle was similar to stainless steel (Kulkarni et al. 1971).

Levels of arterial blood L- and D-lactate were determined in rabbits after SR-PDLLA and SR-PLLA intramedullary nailing. No significant increase in the blood L- or D-lactate levels were observed (Vasenius et al. 1992).

In an experimental study, poly-L/DL-lactide pins were compared with co-polymer poly-L/DL-lactide (70/30) with b-tricalciumphosphate (10%); no different reaction in synovial

membrane, lymph nodes, or bone formation was observed with either polymer. Complete degradation of both materials occurred within 36 months. The implant channel had filled with cancellous bone or scar tissue. The presence of beta-tricalciumphosphate did not elicit more bone formation (Prokop et al. 2004).

2.2.5. Mechanical properties of polylactide

It has been proposed that the strength of an implant needs to exceed the strength of cortical bone for safe fracture fixation (Törmälä et al. 1998). The first PLA implants were produced by extrusion or injection melt moulding techniques, which resulted in bioabsorbable polymers with strength values only typically 40-140 MPa, thus being inferior to those of cortical bone (Table 1).
With the self-reinforcing manufacturing technique, the initial bending strenth of SR-PLLA screws and rods may be increased up to 240 MPa and the shear strength up to 156 MPa (Pohjonen and Törmälä 1996), which is sufficient for bone fixation.

Non-reinforced poly-L/DL-lactide 70:30 implants (Rehm et al. 1994) were introduced in 1994. Their mechanical properties were not suitable for bone fixation: bending strength was 152-163 MPa (Claes et al. 1996, Prokop et al. 2005a).

2.3. PREVIOUS STUDIES

2.3.1. Experimental studies

2.3.1.1. Polyglycolide

PGA rods have been used in the bone fixation in animal experiments since 1982. Subsequently, PGA/PLA copolymer rods have been used experimentally and clinically in bone fixations since 1984. PGA thread was used in fixation of distal femoral osteotomies in 24 rabbits, of which 23 healed without malposition or instability (Vihtonen et al. 1987). Fixation properties of SR-PGA have proved to be sufficient for experimental fractures of cancellous bone (Vainionpää et al. 1986, Vasenius et al. 1994), and also for diaphyseal bone in growing dogs (Miettinen et al. 1992). SR-PGA rods have also been used in experimental osteochondral femoral fractures of sheep (Weiler et al. 1996).

2.3.1.2. Polylactide

Polylactide implants have been successfully used in numerous experimental osteotomies (Majola et al. 1991, Viljanen et al. 1995, Matsusue et al. 1995, Nordström et al. 2001). The less crystalline stereo-copolymers of L-lactide with D- or DL-lactide presented below have been studied also.

Cutright et al. (1971) used PLA sutures for fixation of mandibular symphyseal fractures and later Cutright and Hunsuck (1972) PLA-sheet to treat orbital floor fractures in rhesus monkeys. The fractures healed in a normal manner, and the inflammatory response was minimal, as characterized by the failure to detect phagocytic or giant cells.

Getter et al. (1972) treated fractures in mandibles of six beagles using biodegradable PLA plates and screws. At 32-40 weeks, the fracture sites were indistinguishable histologically from adjacent bone (Getter et al. 1972).

Christel et al. (1982) manufactured biodegradable plates consisting of PLLA embedded with PGA-fibers for added strength. Limited success was achieved using these plates in the internal fixation to treat tibia fractures of sheep (Christel et al. 1982).

Poly-DL-lactide rods were used in mandibular fractures of dogs with acceptable results. In the follow-up, the PDLLA pins had disappeared from the fracture site at 8 months (Kulkarni et al. 1971).

15 mandibular fractures of dogs were fixed with P-L/DL-LA 90:10 plates and screws with good results (Gerlach et al.1987).

Majola et al. (1995) fixed diaphyseal osteotomies in rabbits with self-reinforced P-L/DL-LA 60:40 implants. The degradation time of the implants was 4.5 years.

In an *in vitro* study of implants made of injection-moulded SR-P(L/DL)LA 70:30 with an initial bending strength of 116 MPa, the implants retained their mechanical properties for 36 weeks after which a steady decline in the bending strength was observed (Claes et al. 1996). Amorphous SR-P(L/DL)LA 70:30 plates together with metallic miniscrews were suitable for fixing antebrachial fractures in 10/11 dogs (Saikku-Bäckström et al. 2005). Cortical bone osteotomies in rabbits were successfully fixed with intramedullary self-reinforced fibrillated poly-96L/4D-lactide (SR-PLA96) rods, which disappeared almost totally within three years. For the first 24 weeks the shear strength remained close to the initial level, and at 48 weeks there was no relevant strength of the implant left (Saikku-Bäckström et al. 2001).

Prokop et al. (2004) studied experimentally poly-L/DL-lactide pins and co-polymer poly-L/DL-lactide (70/30) with b-tricalciumphosphate (10%), and noticed a good applicability and complete degradation of both materials within 36 months.

2.3.2. Clinical studies

2.3.2.1. Fixation of ankle fractures

Ankle fracture is one of the most common musculoskeletal injuries, and the incidence of this injury is increasing (Barrett et al. 1999). Unstable ankle fractures usually are managed with open reduction and internal fixation (Weber and Colton 1991, Rüedi 2000). Restoration of the normal anatomy and especially the talar position under the tibia yields better outcomes than can be achieved with a closed treatment with poor anatomic position (Phillips et al. 1985).

Metallic plates and screws have been mainly used in the internal fixation of fractured malleoli (Rüedi 2000, Michelson 2003, Phillips et al. 1985). Reliable cancellous bone fixation is achieved with metallic devices, but the disadvantages of rigid implants are stress-protection atrophy and porosis of bone (Paavolainen et al. 1978, Rosson and Shearer 1991, Tonino et al. 1976) and possible discomfort and pain caused by subcutaneous implants, which may need to be removed in a second operation. Significant complications occurred following the implant removal in 19 % of operations (Brown et al. 1993).

The results of the operative treatment of unstable ankle fractures are generally good. In a series of 306 dislocated ankle fractures treated with metallic implant fixation, the functional results were good in 82 % of patients, acceptable in 8 %, and poor in 10 % after six years of follow-up. The most common complications were post-traumatic arthritis (14 %), infection (1.8 %), and wound margin necrosis (3.2 %). A total 84 % of male patients attained an excellent or good clinical result whereas only 72 % of female patients attained this result (Lindsjö 1985). In another study, 15 surgically treated Lauge-Hansen (1950) pronation external-rotation type IV ankle fractures were treated by open reduction and internal fixation with metallic plates and screws. Anatomical reduction and bony union were achieved in all ankles. The outcome result was analyzed on average 71 months post-operatively. Mild osteoarthritic changes occurred in seven with moderate changes in one

ankle. The best clinical results were achieved in men under 40 years of age (Stiehl and Schwartz 1990).

2.3.2.2. Hallux valgus

Hallux valgus is a common trouble in western countries – wearing of constricting and high heel shoes is considered to be a major cause in the development of hallux valgus. Additionally, heredity plays a significant role, and up to 68 % of patients have a familial tendency to develop this disorder (Glynn et al. 1980).

The complex biomechanics of the foot and especially the first ray may be disturbed leading to proximal phalanx lateralisation (hallux valgus), metatarsal medialisation (metatarsus primus varus), weakening on the medial side of the first metatarso-phalangeal (MTP) joint, erosion of the plantar ridge of distal metatarsal, lateral dislocation of sesamoids, flexors and extensors, contracture of adductor hallucis and lateral capsule, dorsiflexion and pronation of hallux, and eventually insufficiency of the first ray and overload of the lesser rays (Robinson and Limbers 2005). Some authorities believe that the hypermobility of the first tarsometatarsal (TMT) joint is a significant factor in the aetiology of hallux valgus and metatarsus primus varus (Hansen 2000, Myerson and Badekas 2000).

More than 130 techniques have been described for the operative treatment of hallux valgus, and it is apparent that no single procedure is perfect, and none will suit all cases (Robinson and Limbers 2005). However, in terms of the operative treatment, there is evidence that surgery (chevron osteotomy) in mild hallux valgus disease (hallux valgus angle $\leq$ 35 degr, intermetatarsal angle $\leq$ 15 degr) achieves significantly better results than conservative treatment (orthosis or no treatment) (Torkki et al. 2001).

2.3.2.3. Clinical studies on bioabsorbable implants

The human mandibular fractures were the first fractures to be fixed with bioabsorbable PGA sutures with an intraoral arch bar (Roed-Petersen 1974).

In orthopaedics and traumatology, bioabsorbable fixation devices have been used since 1984, initially in ankle fractures (Rokkanen et al. 1985). SR-PGA or co-polymer SR-PGA/PLLA were used as the implant material in the first studies (Ahl et al. 1994, Böstman

et al. 1990, Hirvensalo et al. 1991, Rokkanen et al. 1985). PLLA has been used as an implant material since 1988 (Bucholz et al. 1994, Eitenmüller et al. 1996, Partio et al. 1992a, Partio et al. 1992b, Partio et al. 1992c, Pihlajamäki et al. 1994, Voutilainen et al. 2002).

The SR-PLLA screw has been proven to be a safe and efficient alternative in the treatment of ankle fractures. The pioneering work of the groups of Törmälä and Rokkanen introduced the SR-PGA implant as being applicable for ankle fractures. Comparable results could be obtained using either metallic or SR-PGA-PLA-copolymer implants (Böstman et al. 1987). The SR-PLLA screw has been found to be a safe and efficient in fracture fixation in one long term evaluation (Voutilainen et al. 2002). Good results have been obtained with bioabsorbable screws in the syndesmosis fixation (Hovis et al. 2002, Kaukonen et al. 2005, Korkala et al. 1999, Sinisaari et al. 2002, Thordarson et al. 2001). The SR-PLLA screw has been used also for more mechanically demanding purposes, such as in fixation of femoral neck fractures (Jukkala-Partio et al. 2000).

PLLA implants have exhibited good biocompatibility in a score of clinical short-term studies in orthopaedics and traumatology (Barca and Busa 1997a, Barca and Busa 1997b, Böstman et al. 1995, Jukkala-Partio et al. 1998, Juutilainen et al. 1995, Juutilainen and Pätiälä 1995, Matsusue et al. 1996, Partio et al. 1992c, Partio et al. 1992d, Pihlajamäki et al. 1994, Tuompo et al. 1997, Tuompo et al. 1999a, Tuompo et al. 1999b).

The same good biocompatibility has been observed with P(L/DL)LA implants in craniomaxillofacial surgery, as reviewed by Ashammakhi et al. (2001). As the degradation time of PLA in living organisms is several years, only studies with follow-up intervals of more than 4 or 5 years are valid for determining the ultimate biocompatibility of PLA implants (Ashammakhi et al. 1999).

There are several orthopaedic studies into the long-term high biocompatibility of SR-PLLA, indicating that SR-PLLA material degrades inside the bone within 4-6 years, leaving behind channels filled with connective tissue-dense material, and with cortical bone-dense margins. Slight bone resorption occurred, but there was no vigorous osteolysis (Voutilainen et al. 2001, Voutilainen et al. 2002).

No foreign-body tissue reactions occurred in another orthopaedic clinical study with a follow-up mean time 5.3 years (range 4-9), which is sufficiently long to determine the biocompatibility of non-reinforced PLLA (Matsusue et al. 1997).

Limited soft tissue envelope and the unnecessarity of a second operation to remove implants have increased the popularity of bioabsorbable internal fixation devices in podiatric surgery (Caminear et al. 2005, Claes et al. 1996, Hirvensalo et al. 1991, Porter and Anderson 2004, Barca and Busa 1997a, Barca and Busa 1997b, Clare and Walling 2004, Raikin and Ching 2005, Rokkanen et al. 2000). Caminear et al. used poly-L-lactic acid/polyglycolic acid (82:18) copolymer implants to fix distal chevron osteotomies in 15 patients (18 feet). One patient developed postoperatively a giant cell granuloma needing debridement (Caminear et al. 2005).
Mechanically more demanding podiatric procedures, such as proximal metatarsal osteotomy, still have mainly been operated on using metallic implants. However, Clare and Walling (2004) described a technique of bioabsorbable fixation also in proximal metatarsal osteotomies.
In a recent study, SR-PLA70 screws were used in the fixation of 1st metatarso-phalengeal joint arthrodesis in rheumatoid arthritis patients with good results in 8/9 patients (Voutilainen et al. 2002).

2.3.2.4. Complications with bioabsorbable implants

2.3.2.4.1. Experimental studies

In experimental animal studies, PGA and PLA implants have been found to be safe. Clinically detectable tissue reactions – sinus formation or hydrops near the implant – have been very rare (Böstman and Pihlajamäki 2000b), but a late foreign-body tissue reaction to PLLA implant was noted in one rat followed for 143 weeks (Bos et al. 1991). In another study, Räihä et al. (1990) used 4.5 mm SR-poly-L/DL-LA 50:50 screws to fix trochanteric osteotomies in beagles, and noticed 2 of 6 dogs to develope cysts of clear fluid around the implant heads within 8 weeks.

Unexact reduction or nonsatisfactory healing of metaphyseal osteotomies has also been detected. Vihtonen et al. (1988) noticed delayed union or nonunion in 7/24 rabbits distal femoral osteotomies fixed with PGA thread. Manninen et al. (1992) fixed 10 olecranon osteotomies of sheep with SR-PLLA screws and other 10 osteotomies with metallic screws.

2 of 10 osteotomies in SR-PLLA group failed whereas osteotomies with metallic screws maintained fixation. Majola et al. (1991) fixed osteotomies of 56 rats distal femur with SR-PLA80 or SR-PLLA implants. In macroscopical evaluation, there were two unstable specimens at one week and one non-union at 36 weeks after the operation in the SR-PLA80 group. All 28 osteotomies fixed with SR-PLLA implants were firm.

Especially in the rodents, the Oppenheimer phenomenon (Oppenheimer et al. 1955), *i.e.* the tendency to develop sarcomatous lesions around foreign-body material in long-term follow-ups independent of the chemical nature of the implants, has been noticed in a study concerning PLLA and polyethylene blocks implanted subcutaneously for 2 years (Pistner et al. 1993). This phenomenon has not been detected in other animal or human studies.

2.3.2.4.2. Clinical studies

In clinical trials, bioabsorbable implants have been detected to conclude in undesired foreign body reactions, and good biocompatibility of experimental animal studies cannot be directly extrapolated to humans (Böstman and Pihlajamäki 2000b). PGA has been found to be accompanied with foreign body reactions in 3% – 60% in different series (Ambrose and Clanton 2004), and in the largest published series the rate was 5% of the operations (Böstman and Pihlajamäki 2000a). Hirvensalo et al. (1989) reported the transient sterile fluid accumulation to occur in 6/41 ankle fracture patients at an average time of 3 months after insertion of the PGA rods. Böstman et al. treated 102 patients with displaced ankle fractures using PGA rods. In six patients, a sinus formation yielding remnants of the degrading implant was seen at two to four months after the operation (Böstman et al. 1989). Böstman et al. reported a high incidence of adverse tissue reactions (19/105) in ankle fracture patients who were operated on using polyglycolide screws that were colored with an aromatic quinone dye (Böstman 1992c). In another study, unstable medial malleolar fractures were fixed with 4.5-mm polyglycolide screws in 21 patients. 16 patients were followed-up and eight of these developed an inflammatory reaction to the PGA screw at 3 to 4 months after the implantation (Hovis and Bucholz 1997). In a large review, several risk factors for adverse tissue reactions to bioabsorbable fixation devices have been listed: presence of quinone dye, an implant with a large surface area such as a screw, and implant sites with low vascularity such as the scaphoid were all found to be related to a higher incidence of adverse tissue responses (Böstman and Pihlajamäki 2000b). However, the risk of adverse tissue reactions have declined the use of PGA

implants during the recent years in favour of implants made of PLLA, material which have proved to conclude infrequently in clinically relevant foreign-body reactions (Ambrose and Clanton 2004).

Clinically manifest foreign body reactions with PLA have mainly been noticed in extra-osseous use. Foreign body reactions with nonreinforced PLLA were reported in nine of ten patients when extraosseous as-polymerized PLLA plates and screws were used in zygomatic fractures (Bergsma et al. 1995b). The foreign body reactions occurred within 5 years, manifested as a painless swelling at the site of implantation. In another study, nonreinforced PLLA plates were used for ankle fractures in 19 patients. Clinically detectable foreign body reaction (fluid accumulation) of the implant site occurred in 10 patients one year after the operation (Eitenmüller et al. 1996). The intraosseal use of a SR-PLLA implant has been described to cause a foreign body reaction in a bimalleolar fracture patient who developed a macrophage and giant cell-mediated reaction at the site of the lateral malleolar screw head more than four years post-operatively (Böstman and Pihlajamäki 1998). The screw head had not been cut to the bone surface. Bucholz et al. (1994) reported on one clinically detected foreign body reaction and sinus formation in a series of 83 patients with PLLA screw fixation in ankle fractures. The patient had a cyst, which was removed 15 months after implantation of two screws to fix a medial malleolar fracture. In a long-term study, foreign-body reactions were detected in five of sixteen patients in ankle fractures fixed with SR-PLLA screws. In the revision operations of three patients, the palpable masses from operated medial malleoli were removed at 40 – 45 months postoperatively, and softened screw head masses were situated extra-cortically.

Isomeric forms of PLA have been described to conclude in foreign body reaction complications only in soft-tissue fixations, like in ACL reconstructions or rotator cuff reinsertions (Ambrose and Clanton 2004). There exist no reports of adverse tissue reactions in metaphyseal bone fixation with stereoisomeric forms of SR-PLA.

Further, osteolytic changes in bone tissue surrounding the PLA implants have been also reported, but these reactions have had no effect on clinical result (Matsusue et al. 1997, Kallela et al. 1999).

Bioabsorbable devices can provide the necessary initial strength for orthopedic applications as long as the application is chosen with care, and the strength reduction during degradation is slow enough to allow tissue healing (Ambrose and Clanton 2004). In a series published by Juutilainen et al. (2002) SR-PLLA implants were used in 1043 orthopaedic and traumatologic operations: failure of fixation was seen in 46 patients (4.4 %).

The infection rate after ankle fractures was studied and no statistical difference between bioabsorbable (3.2 %) and metallic (4.1 %) implants could not be noticed (Sinisaari et al. 1996). However, depending on the bioabsorbable material used, the infection rates varied from 0.7 % (SR-PLLA) to 6.5 % (SR-PGA and SR-PLLA together).

3. THE PRESENT STUDY

3.1. AIMS

The aims of the present study were to answer the following questions:

1. Are the biocompatibility and fixation properties of SR-P(L/DL)LA 70:30 (SR-PLA70) pins sufficient for fixation of rat distal femoral osteotomy?

2. Are the biocompatibility and fixation properties of drawn SR-PGA pins sufficient for fixation of rat distal femoral osteotomy?

3. What are the strength retention times of SR-PLA70 and drawn SR-PGA pins?

4. Is it possible to fix reliably the ankle fracture with SR-PLA70 and SR-PLLA screws?

5. Is it possible to fix reliably the first proximal metatarsal osteotomy or tarsometatarsal arthrodesis in hallux valgus deformity with SR-PLA70 and SR-PLLA screws?

3.2. OVERVIEW OF STUDIES

A brief overview of Studies I-IV is presented in Tables 3 and 4.

Table 3. Overview of experimental studies.

Study			No. of animals	Methods
Experimental	I	SR-PLA70 rods in vivo subcutaneously and in rat femur osteotomies	16+38	Strength measurements of rods Radiology, histology, histomorphometry, microradiography, and oxytetracycline-fluorescence
Experimental	II	SR-PGA rods in vivo subcutaneously and in rat femur osteotomies	16+39	

Table 4. Overview of clinical studies.

Study			No. of patients	Methods
Clinical	III	SR-PLA70 and SR-PLLA screws in ankle fractures	62	Clinical examination, radiography, and Olerud-Molander score
Clinical	IV	SR-PLA70 and SR-PLLA screws in proximal hallux valgus corrections	25	Clinical examination, radiography, and AOFAS-score

3.3. IMPLANTS

The bioabsorbable SR-PGA, SR-PLA70 and SR-PLLA rods and screws used in the present study were manufactured by the Institute of Biomaterials, Tampere University of Technology, Tampere, and Bionx Ltd. (nowadays Linvatec Biomaterials Ltd.), Tampere, Finland, with the self-reinforcing technique (Törmälä et al. 1987, Törmälä 1992).

3.3.1 Drawn self-reinforced polyglycolide pins (II)

The polymer used for the rods was a commercially available medical grade polyglycolide (Purasorb-PGA, MFI at 230 °C, manufacturer CCA Purac, Holland). The rods were manufactured in Bioscience Ltd., Tampere, Finland using a die-drawing technique. The nominal diameter of the rods was 2.0 mm. The length of the pins used in mechanical tests was 26 mm and 15 mm in osteotomy fixations. The pins were sterilized with ethylene oxide.

3.3.2. Self-reinforced poly-L/DL-lactide 70:30 pins (I)

The polymer used for the pins was a commercially available medical grade poly-L/DL-lactide 70:30 having an inherent viscosity of 5.7 dl/g (Resomer® LR 708 lot 250773 from Boehringer Ingelheim, Ingelheim am Main, Germany). In the pin, the SR-PLA70 acronym, 70 stands for 70 % of L-lactide and the remaining 30 % consists of D/L-lactide. The pins were manufactured in the Institute of Biomaterials, Tampere University of Technology, Tampere, Finland using a die-drawing technique. The nominal diameter of the pins was 2.0 mm. The lengths of the pins used in mechanical tests were 26 mm and 15 mm in osteotomy fixations. The implants were gamma-sterilized with a nominal dose of 33 kGy.

3.3.3 Self-reinforced poly-L-lactide screws (III and IV)

The full-threaded SR-PLLA screws (Bionx Implants Ltd., Tampere, Finland) used in studies III and IV were 35, 50 or 70 mm long and 4.5 mm in outer diameter and 3.2 mm in core diameter. The screws were manufactured of PLLA with an initial raw material MW of 250 000 to 727 000.

3.3.4 Self-reinforced poly-L/DL-lactide 70:30 screws (III and IV)

The full-threaded SR-PLA70 screws (Bionx Implants Ltd., Tampere, Finland) used in studies III and IV were 35, 50 or 70 mm long and 4.5 mm in outer diameter and 3.2 mm in core diameter.

The screws were manufactured of a mixture of PLLA and racemic DL-lactide with an initial raw material MW of 450 000 daltons.

3.3.5 Self-reinforced poly-L-lactide pins (III and IV)

SR-PLLA pins 50 mm long and 2.0 mm in diameter were used in studies III and IV for additional fixation, when needed.

The pins were manufactured of PLLA with an initial raw material MW of 250 000 to 660 000 daltons.

3.4. EXPERIMENTAL STUDIES (I and II)

3.4.1. Material and methods

The Ethical committee for Animal Experiments of Helsinki University Central Hospital approved the plan of the present experimental studies before starting the investigations (approval n:o 1227/712-86).

A total of 109 female Wistar rats were used in the present study (Table 5).

Table 5. Plan of experimental studies on rats.

Schedule of self-reinforced poly-L/DL-lactide 70:30 (SR-PLA70) and self-reinforced polyglycolide (SR-PGA) pin fixation of osteotomies in cancellous bone of rats									
Characteristics	Number of rats followed up								
	Weeks								
	1	3	6	12	24	36	48	52	Total
Histologic studies									
SR-PLA70	4	5	5	5	5	5	5	5	39
SR-PGA	5	5	5	5	5	5	5	3	38
Total number of osteotomy studies									77
Strength studies									
SR-PLA70	2	2	2	2	2	2	2	2	16
SR-PGA	2	2	2	2	2	2	2	2	16
Total number of strength studies									32
Total number of rats									109

Experimental animal care complied with the guidelines of the national law on the care and use of laboratory animals. The rats were anaesthetized for induction with CO2 by inhalation, and the anaesthesia was continued with 0.1 mg per 300 g medetomidine (Domitor®, Lääkefarmos, Turku, Finland) and 3 mg per 300 g ketamine hydrochloride (Ketalar®, Parke-Davis, Barcelona, Spain) by subcutaneous injection. Postoperatively, the rats were given 100 000 IU procaine penicillin s.c. for infection prophylaxis.

3.4.2. Operative techniques

3.4.2.1. Subcutaneous implantation of the rods in rats in the mechanical tests

A total of 32 rats were operated on prior to the mechanical studies. Four bioabsorbable rods, 26 mm long, were implanted in the dorsal sucutaneous tissue through 4 separate surgical approaches. The wounds were closed with a 4-0 USP PGA sutures (Dexon®, Davis+Geck, USA). Postoperatively the rats were returned to their cages, where they recovered from anaesthesia. They were fed a regular normal laboratory animal diet. They were followed-up for 1, 3, 6, 12, 24, 36, 48 and 52 weeks.

After sacrifice of 32 rats, 4 in each follow-up time, the rods were removed from the dorsal subcutaneous tissue of rats, and immediately placed in saline. The bending strength tests were determined for the wet rods within 19 h after death and immediately after removal from saline.

3.4.2.2. Osteotomy fixation in rats

A total of 77 rats were operated with an osteotomy of the femur. The right knee was shaved and sterilized with antiseptic fluid (Neo-Amisept®, Orion-Farmos, Turku, Finland). An incision was made through the medial side to open the knee. The patella was dislocated laterally and the distal end of the femur was exposed. A 2 mm drill hole was made through the intercondylar space. An osteotomy was performed using an oscillating saw through the metaphysis, leaving the posterior cortex intact to serve as a hinge. A drawn SR-PGA rod, 15 mm long was introduced through the drill hole to fix the osteotomy (Fig. 5). The wounds were closed in layers with a 4-0 USP PGA sutures (Dexon, Davis+Geck, USA) and the rats were given 100 000 IU procaine penicillin s.c.. Postoperatively the rats were returned to their cages, where they recovered from anaesthesia. They were fed a regular normal laboratory animal diet. The rats were allowed to use their limbs after the operation, and no external support or splint was used. They were followed-up for 1, 3, 6, 12, 24, 36, 48 and 52 weeks; and each study follow-up group consisted of five rats, except at the fifty-two week time point which consisted of three rats. Two days prior to sacrifice, the rats were given oxytetracycline 50 mg/kg to make newly formed bone visible for oxytetracycline (OTC) labelling studies. The rats were sacrificed with an overdose injection of medetomidine and ketamine. The healing of the osteotomies

was evaluated radiologically, histologically, microradiographically, histomorphometrically and by examining the oxytetracycline fluorescence.

3.4.3. Examination methods

After sacrifice, both femurs were disarticulated and dissected in each rat. Radiographs were taken in the anteroposterior and lateral position (distance 100 cm, 40kV, 12 mA and 0.03 seconds) with a macroscopic and manual evaluation of the osteotomies. The intact left femur acted as a control. The distal parts of both femora were taken as specimens, fixed in ethanol and embedded in methyl-methacrylate. For the histological analysis, five micrometer thick longitudinal sections in the coronal plane were cut with a microtome (Polycut S, Reichert-Jung, Nussloch, Germany) and stained by a modified Goldner-Masson method (Goldner 1938). Sections measuring 80 micrometer were cut with a Leitz Saw Microtome 1600 (Leitz GMBH, Wetzlar, Germany) for the OTC-fluorescence and microradiographic studies. In the microradiographic examinations, Kodak Professional film SO 343 was used, and the technical values were: 50 kV, 9 mA, 12-min of exposure time, and a 22 cm film-focus distance. Fluorescence microscopy was performed using a HBO 220 UV lamp and a BG 812/6 primary filter.

In the semiautomatic quantitative histomorphometric analysis, a Leitz microscope was linked via a videocamera (PCO, SensiCam 3.0, Kelheim, Germany) to a computer (Dell Optilex MMP Pentium, Ireland). Magnifications of 20 x and 125 x were used with Image analyzing software (AnalySIS Pro 3.00, Soft-Imaging Software GmbH, Münster, Germany). Six specimens and control femurs in seven follow-up groups (from 1 to 48 weeks) were analyzed, with the exception of the 3 weeks and 48 weeks groups, which included five and four rats, respectively. There were 80 longitudinal histological sections, and from each, four standardized sample fields (320 altogether) were delineated in the femurs at the metaphysis centralizing 6.0 mm from distal joint level and 1.5 mm apart in a horizontal direction (Fig. 5). In every specimen, the AnalySIS-program was used in the determination of the corresponding site.

The histomorphometric variables were analyzed within the 1.06 mm x 0.84 mm (0.89 mm^2) sample fields. The variables examined were as follows: total trabecular bone volume fraction (including calcified trabeculae and osteoid), total osteoid surface fraction over the entire trabecular surface, and active osteoid formation surface fraction over the total trabecular surface. Ongoing calcification of the osteoid was confirmed by fluorescence microscopy and microradiography.

In the OTC studies, osteotomized femurs were microscopically systematically analyzed in 10 different areas as presented in a schematic picture (Fig. 5). Areas 1-4 represent subperiosteal region, areas 5-8 represent intraosseal bone near to the implant, area 9 represents intraosseal bone near the osteotomy, and area 10 represents intraosseal bone proximal to the implant. From each area, the intensity of fluorescence was evaluated and grading 0-3 was used (0 = none, 1 = weak, 2 = moderate, 3 = marked). The mean of grade of intensity was calculated for areas 1-4, 5-8, 9 and 10. The areas were analyzed as measured variables, not as ranked variables.

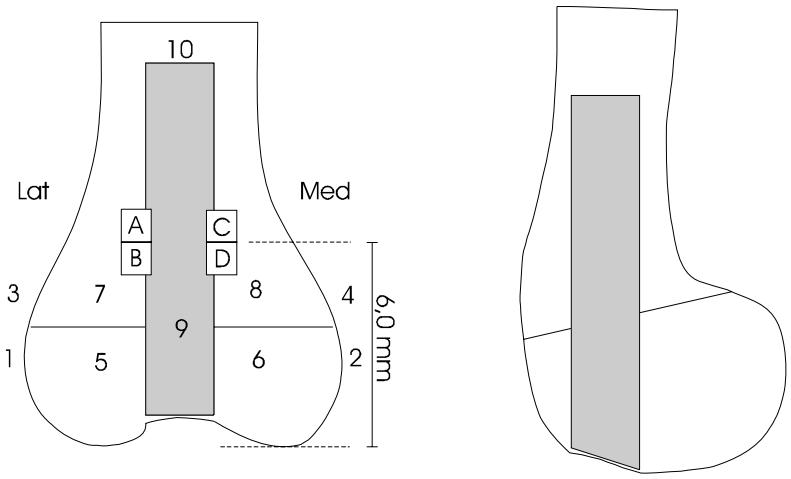


Figure 5. Schematic anterior and lateral views of the distal rat femur showing the site of the osteotomy, the implant, the four standardized sample fields (A, B, C, D) and the ten areas (1-10) analyzed in oxytetracycline fluorescence study. 1 to 4 represent subperiosteal region, 5-8 intraosseal region, 9 near implant and area 10 represents the area proximal to the implant. (I)

3.4.4. Statistical methods

In the statistical analysis, one-way analysis of variance was used in the preliminary evaluation of time-related differences of histomorphometric variables. In the final analysis, regression analysis and paired t-test were employed. Kruskal-Wallis test and Tukey's HSD test were used in the oxytetracycline labeling results. Tukey's HSD tests were confirmed with Fisher's exact test.

3.4.5. Results of experimental studies

A total of 109 rats were operated. None of the 32 rats used in the subcutaneous implantation of SR-PLA70 or SR-PGA pins for mechanical tests experienced any complications. Seventy-seven rats had undergone osteotomy fixation. Seven specimens on the SR-PLA70 group and five specimens in SR-PGA group had to be excluded when evaluating the results. The criteria of exclusion were as follows: in five rats (one at 3 weeks, one at 36 weeks, two at 48 weeks, and one at 52 weeks) infection (swelling and odour) at the time of sacrifice, in one rat (3 weeks) failure and redislocation of the osteotomy, in one rat a missing condyle resembling avascular necrosis of the femur, in four rats (one in 48 weeks, three in 52 weeks) a non-union of the osteotomy on macroscopic, radiographic and histological analysis of the specimen, and in one rat (1 week) failure of fixation and redislocation of the osteotomy were noticed.

3.4.5.1 Mechanical and material testing

The results of mechanical testing are presented in the Table 6.

The initial flexural strength of the drawn SR-PGA pins was 270 +- 30 MPa and flexural modulus was 13 +- 2 GPa. At 3 weeks in vivo, the flexural strength and modulus of the SR-PGA rods were 144 +- 29 MPa and 6 +- 0.5 GPa, respectively. At 6 weeks in vivo, the SR-PGA rods had lost their strength totally.

The initial flexural strength of the SR-PLA70 pins was 214 +- 4 and the flexural modulus was 6.0 +- 0.5 GPa. The strength decreased slowly: at 52 weeks the flexural strength was 43% and the flexural modulus was 41% of the initial value.

In the scanning electronmicrographic (SEM) examination, the first signs of degradation were seen on the surface of the SR-PGA rods at one week and on the SR-PLA70 rods at 24 weeks *in vivo*. At three weeks, the drawn SR-PGA pins started to lose their reinforced structure seen by the appearance of lamellar structures on the surface and below it, and at six weeks, the surface layer had peeled off and the reinforced structure was completely lost. At 36 weeks, the SR-PLA70 rods started to lose their reinforced structure, this being visible as lamellar structures on the surface and below it. The solid surface started to peel,

showing subsurface porosity and lamellae. At 52 week, the reinforced structure was completely lost and porosity had developed further.

Table 6. Results of material testing of SR-PLA70 and drawn SR-PGA pins.

	Weeks								
	0	1	3	6	12	24	36	48	52
SR-PLA70									
Bend strength (MPa)	214	214	202	200	198	168	167	72	94
Shear strength (MPa)	121	116	84	119	113	110	95	73	50
Elastic modulus (GPa)	6,0	4,6	4,2	5,8	5,7	3,6	3,8	2,6	2,5
SR-PGA									
Bend strength (MPa)	270	216	144	0	0	0	0	0	0
Elastic modulus (GPa)	13	10	6	0	0	0	0	0	0

3.4.5.2 Radiology

The implant channel could be seen throughout the one year follow-up in all but three of the specimens: two at 36 and 48 weeks in SR-PGA group and one at 52 weeks in SR-PLA70 group. In the radiographs some dislocations of fixation in the osteotomies could be seen: four in SR-PGA group (two at three weeks, two at six weeks) and two in SR-PLA70 group (on at 3 weeks, one at 48 weeks).

One to three weeks

The osteotomy line could be seen in two of ten specimens (one specimen at one week in both study groups). There was a slight external callus formation at one week and significant callus formation at three weeks.

Six weeks

The amount of external callus had decreased when compared to the three weeks' specimens. Seven of ten specimens were at least partially visible, three osteotomies could not be seen in the SR-PGA specimens.

12 weeks

The osteotomy lines were hardly visible in three of ten osteotomies. At the osteotomy site external callus formation was seen in three radiographs. All ten osteotomies were consolidated without angular deformity.

24 weeks

All ten osteotomies were consolidated. The osteotomy line was not visible in any radiograph. The amount of external callus had decreased.

36 weeks

Remodelling of the bony callus was observed. The distal and proximal parts of the implant channels could be seen in all ten specimens.

48 weeks

The remodelling had advanced. Osteolytic areas of femur condyle were seen in two SR-PGA specimens. The distal and proximal parts of the implant channels could still be seen in all but one of the femurs. In that specimen, the distal SR-PGA implant channel had filled with bone. In the SR-PLA70 specimens, new bone had grown around the implants and the outline of the rods was barely visible in the radiographs.

52 weeks

In two SR-PGA specimens it was possible to detect the osteolytic area. The distal and proximal parts of the implant channels could still be seen in all but two of the radiographs, one in SR-PGA and one in SR-PLA70 specimens.

3.4.5.3 Histological, microradiographic studies

In the histological analysis there were six specimens in the SR-PLA70 group and one specimen in the SR-PGA group displaying signs of infection (neutrophilic leukocyte infiltration near osteotomy or implant channel). The infections occurred at three weeks (two specimens), 48 weeks (two specimens), and 52 weeks (two specimens) in SR-PLA70 group and at 24 weeks (one specimen) in SR-PGA group.

Results of oxytetracycline fluorescence studies are presented in Figure 14.

One to three weeks

The osteotomies were visible in the histological and microradiographic studies (Figure 6b). At three weeks, endosteal and intense periosteal new bone formations were seen around the implant at the osteotomy region. Around the rods, there was a thin rim of regenerative granulation tissue. There was no accumulation of giant cells.

Six weeks

Three osteotomies in SR-PGA specimens and four in SR-PLA70 specimens displayed bony union in the histological and microradiographic studies (Figure 7a-b). The external callus formation had increased, and new bone formation was found around the rods. Proximal and distal implant channel could clearly be seen in the microradiographical and histological sections. Invasion of granulation tissue into the polyglycolide implant was seen, whereas the SR-PLA70 implant area did not include any cells.

12 weeks

All ten osteotomies exhibited bony union (Fig. 9). The histological analysis revealed trabecular bone surrounding the implant. Granulation tissue was noticed between the degraded particles of SR-PGA implant and the trabecular bone. Foamlike macrophages had invaded the SR-PGA implant, and no distal implant channel could be seen in three of five SR-PGA specimens, because the orifice of the implant channel was covered with connective tissue. In the SR-PLA70 specimens, a layer of fibrous tissue was seen between the implant and bone. In microradiographical analysis, the implant channel was not filled with bone in any of the specimens.

24 weeks

Eight of ten osteotomies in both study groups (four SR-PGA, four SR-PLA70) were consolidated histologically (Figure 11a-b). In two femora, there was a partly visible osteotomy line. In four consolidated SR-PGA specimens, new bone and osteoblasts were seen in the former implant channel area, and the implant had degraded into small particles. The orifice of the implant channel could not be seen in any case, and the proximal channel had filled also in four cases. Microradiographically, the implant channels were open in 2 of 5 SR-PGA specimens.

In four consolidated SR-PLA70 specimens, new bone and native bone marrow lay around the SR-PLA70 rods. Microradiographically, the orifice of the implant channels was open.

36 weeks

Five SR-PGA osteotomies exhibited bony union in the histological and microradiographic examination. New bone was seen around the implant channel, and the channel itself had

become filled with fibrous tissue and bone. Microradiographically, the channel could not be seen in any of the five specimens, and there were large amounts of bone inside the femur. Two of the four osteotomies on the SR-PLA70 group showed bony union. New bone was seen around the implant channel.

48 weeks

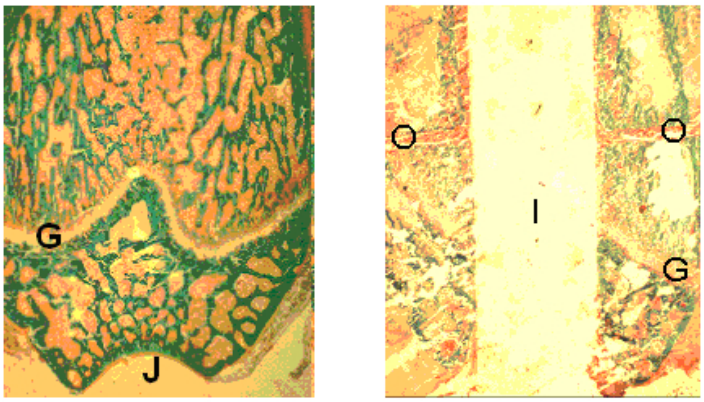
All four SR-PGA osteotomies had consolidated without dislocation, and the osteotomy line could not be seen histologically or microradiographically. The remodelling had advanced. Only bone and connective tissue had replaced the implant,.

In the SR-PLA70 specimens, two of the three osteotomies showed a bony union and one case showed a dislocation and a non-union of the osteotomy. New bone was formed around the implant.

52 weeks

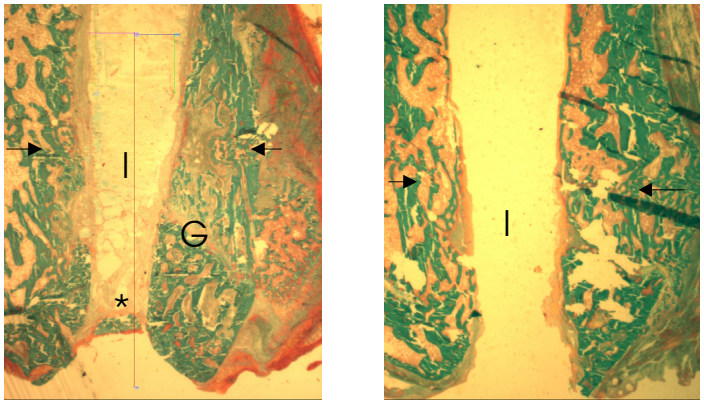
In the SR-PLA70 specimens, prominent bone encircled the implant area. There were no signs of implant breakage.

Figures 6 – 11 of experimental studies. Photomicrographs of rat distal femora at different times. All samples Masson-Goldner.



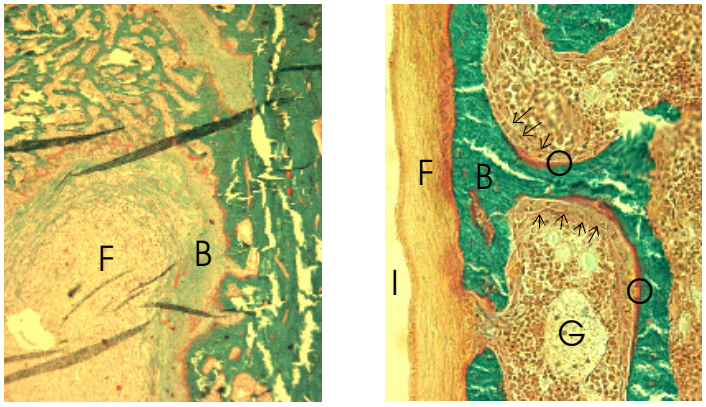
A B

Figure 6. (A) Control femur and (B) SR-PGA at one week. G = growth cartilage, J = joint, O = osteotomy site, I = implant channel. Original magnification 20x.



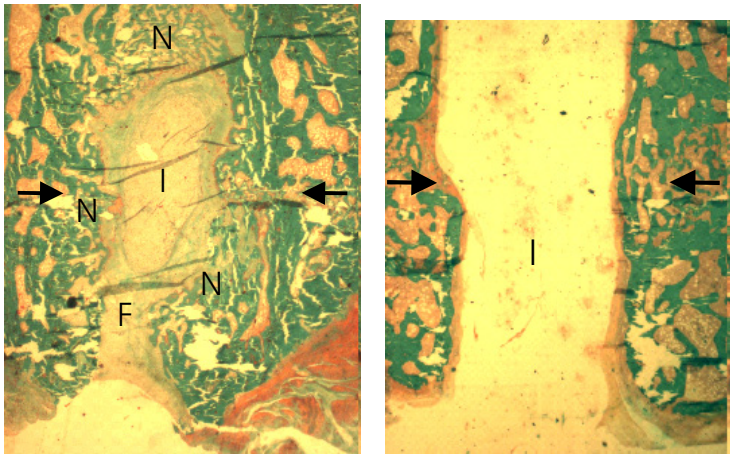
A B

Figure 7. (A) SR-PGA at 6 weeks and 7b SR-PLA70 at 6 weeks. Fibrous tissue invades the SR-PGA implant, whereas SR-PLA implant remains acellular. G = growth cartilage, I = implant channel, arrows = osteotomy site, * = bone and fibrous tissue in the orifice of implant channel. Original magnification 20x.



A B

Figure 8. (A) SR-PGA 12 weeks, original magnification 50x, and (B) SR-PLA70 at 6 weeks, original magnification 300x. Fibrous tissue (F) and new bone (B) has grown from the periphery toward the center in the SR-PGA implant area. A thin fibrous tissue (F) surrounds the intact SR-PLA70 implant (I). Giant cells (G), cube-like osteoblasts (small arrows) and red-staining osteoid (O) on the surface of bone trabeculae (B) is also visible.



A B

Figure 9. (A) SR-PGA 12 weeks (II) and (B) SR-PLA70 12 weeks. Original magnification 20x. Fibrous tissue (F) and new cancellous bone (N) has replaced most of the site of the SR-PGA implant (I), whereas SR-PLA70 implant (I) remains as a solid structure at 12 weeks after the implantation. Site of the osteotomy (arrows) is consolidated in both specimens.

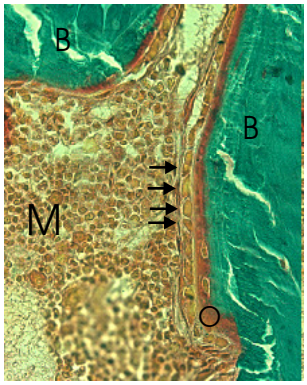
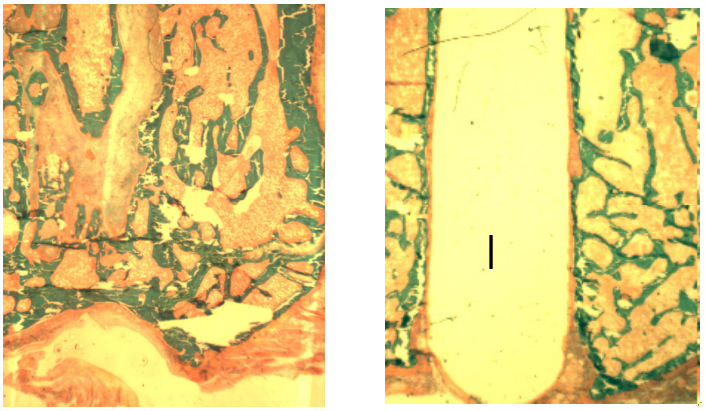


Figure 10. SR-PLA70 at 12 weeks after implantation. Note the bone trabeculae (B), osteoid (O), and osteoblasts (arrows) and active bone marrow cells (M). Original magnification 500x.



A B

Figure 11. (A) SR-PGA 24 weeks and (B) SR-PLA70 24 weeks. SR-PGA implant has been biodegraded and replaced by bone, whereas SR-PLA70 implant (I) remains inside the femur. Original magnification 20x.

3.4.5.4 Histomorphometry

Table 7. Results of histomorphometric analysis of the tissue-implant interface at various times after implantation of drawn self-reinforced polyglycolide acid rod in osteotomized rats' distal femur (mean and standard deviation, SD) (II).

		Time (weeks)						
		1	3	6	12	24	36	48
Total trabecular bone volume fraction of the total tissue volume (%)	Control	38,4	40,0	27,1	35,9	21,7	18,3	32,0
		14,7	12,9	12,7	7,5	10,1	10,2	10,2
	PGA	29,3	42,5	43,4	57,2[1]	44,3[1]	33,0	61,3[2] [4]
		13,2	15,9	19,4	20,1	29,9	22,3	24,3
Total osteoid surface fraction over the entire trabecular surface (%)	Control	3,2	0,9	0,0	0,0	0,0	0,0	0,0
		5,5	2,1	0,0	0,0	0,0	0,0	0,0
	PGA	4,8	14,8[1]	15,7	23,2[3]	33,4[2]	18,4	3,4 [4]
		6,9	19,0	26,1	18,3	33,8	31,4	11,7
Active osteoid formation surface fraction over the total trabecular surface (%)	Control	1,8	0,4	0,0	0,0	0,0	0,1	0,0
		3,4	0,9	0,0	0,0	0,0	0,2	0,0
	PGA	3,5	9,9[1]	5,7	12,7[2]	19,9[1]	9,9	2,5 [4]
		4,8	12,8	9,6	12,3	23,2	22,1	8,8

1: $p < 0,05$ (paired *t*-test compared to control side), 2: $p < 0,01$ (paired *t*-test compared to control side), 3: $p < 0,002$ (paired *t*-test compared to control side), 4: $p < 0.001$(paired *t*-test compared to all controls)

Table 8. Results of histomorphometric analysis of the tissue-implant interface after implantation of SR-PLA70 rods in the osteotomized distal femur of rats (mean and SD) (I).

		Time (weeks)						
		1	3	6	12	24	36	48
Total trabecular bone volume fraction of the total tissue volume (%)	Control	42,4	40,8	33,9	23,6	23,6	20,7	25,6
		14,0	10,8	9,6	11,7	11,4	6,0	15,6
	SR-PLA70	55,4*, ¤	31,9*	46,2*	41,2*, ¤	36,9*, ¤¤	35,0*, ¤¤	15,8*
		12,0	7,8	20,8	13,5	13,0	11,8	23,7
Total osteoid surface fraction over the entire trabecular surface (%)	Control	1,0	0,2	2,4	2,1	1,7	5,8	0,5
		1,3	0,6	3,7	4,1	2,7	7,9	0,9
	SR-PLA70	5,1*, ¤	12,7*, ¤¤¤	21,0*, ¤¤¤	13,0*, ¤	18,4*, ¤¤¤	11,7*	0,0*
		5,3	7,0	10,9	11,8	9,8	6,9	0,0
Active osteoid formation surface fraction over the total trabecular surface (%)	Control	0,2	0,1	0,4	0,3	0,2	0,3	0,2
		0,3	0,2	0,5	0,8	0,3	0,5	0,4
	SR-PLA70	1,3**	2,1**	5,2**, ¤¤	3,1**	5,2**, ¤¤	1,5**	0,0**
		2,0	1,8	4,3	3,8	5,5	2,1	0,0

*p < 0,001 (one-way analysis of variance) ¤ p < 0,05 (paired *t*-test with regard to control)

**p < 0,05 (one-way analysis of variance) ¤¤ p < 0,01 (paired *t*-test with regard to control)

¤¤¤ p < 0,001 (paired *t*-test with regard to control)

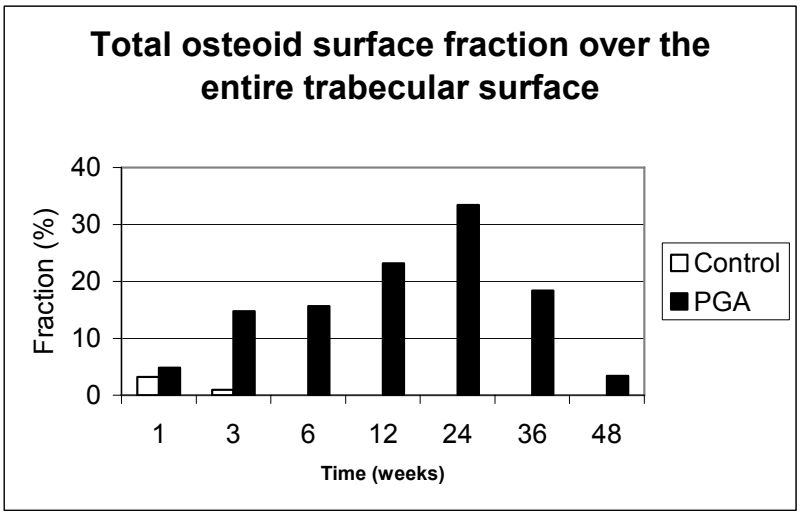


Figure 12.

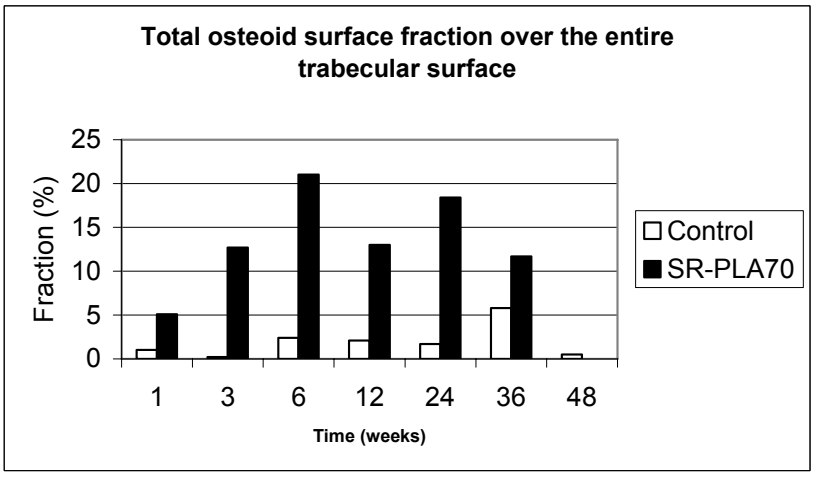


Figure 13.

Figures 12 and 13. The osteoid surface fraction over the total trabecular surface (%) in the distal rat femur 1, 3, 6, 12, 24, 36, and 48 weeks after fixation of an osteotomy with an SR-PGA rod and SR-PLA70.

In the SR-PGA specimens, the total trabecular bone volume fraction exhibited its highest value (61.3 %) at 48 weeks in the osteotomized femora. The total osteoid surface area and the active osteoid formation surface area reached their highest values at 24 weeks (33 %, 20 %). After 24 weeks, the total osteoid surface fraction and the active osteoid formation surface fraction diminished gradually, being 3-4 % and 2-5 % at 48 weeks. According to

the regression analysis, all of the studied variables of the osteotomised femurs were found to be curvilinearly dependent on time in all of the different models.

In the SR-PLA70 specimens, the total trabecular bone volume fraction displayed its highest value at 1 week both in the osteotomised (55 %) and control (42 %) femurs. The total osteoid surface area, and the active osteoid formation surface area reached their highest values at six weeks (21 %, 5 %). After this, both values diminished gradually, being 0 at 48 weeks. In the regression analysis, all of the studied variables of the osteotomised femurs were found to be curvilinearly dependent on time in all of the different models.

OTC fluorescence studies (Figures 14 and 15).
In the SR-PGA specimens, the OTC fluorescence in the osteotomised femurs exhibited the highest intensity representing intense new bone formation during six to 12 weeks in the osteotomy region, subperiosteally, and around the implant. The increase in intensity appeared first in subperiosteal regions at three weeks. After 12 weeks, the OTC fluorescence declined. The subperiosteal area showed both an earlier increase and then a decrease compared to the other areas in OTC fluorescence intensity.

In the SR-PLA70 specimens, the highest intensity was noted from six to 12 weeks. A rapid increase of intensity appeared first in the subperiosteal region at three weeks and the intensity also started to decline first in the subperiosteal regions.

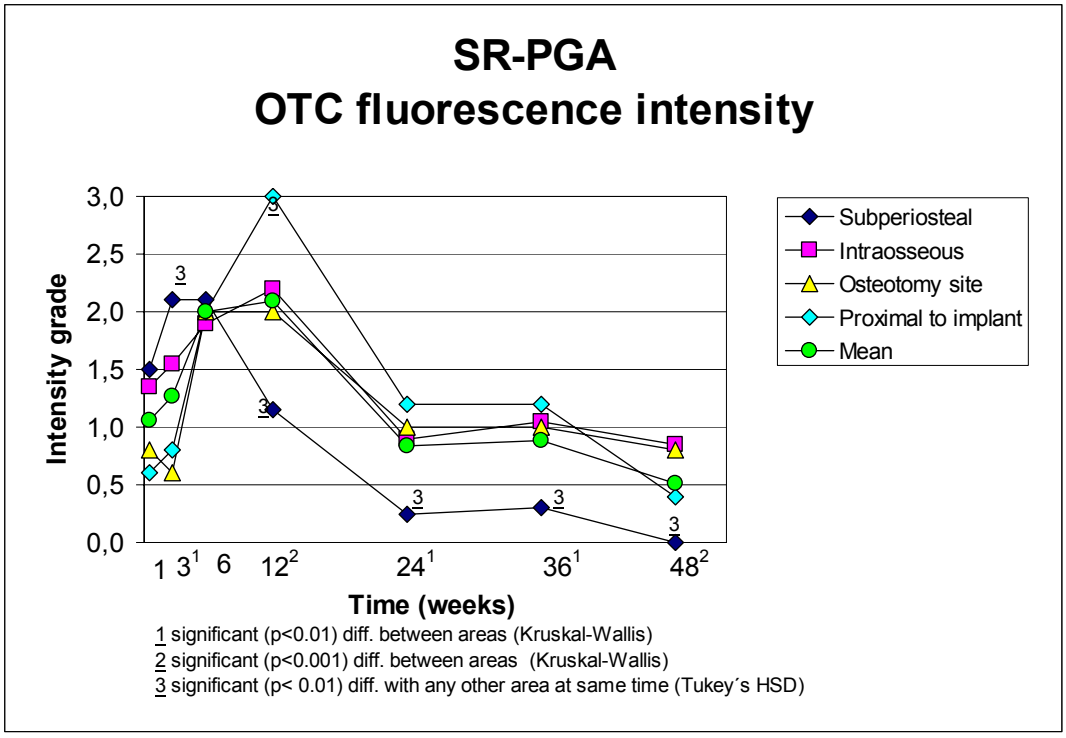


Figure 14. Oxytetracycline (OTC) labelling study results after fixation of the distal femoral osteotomies with SR-PGA-rods. Mean of grades of fluorescence intensity in different areas (0 = none, 1 = minimal, 2 = moderate, 3 = marked). Areas 1-4 represent subperiosteal region, areas 5-8 represent intraosseous bone near the implant, area 9 represents intraosseous bone near the osteotomy, and area 10 represents intraosseous bone proximal to the implant. From each area, the intensity of fluorescence was evaluated and grading 0-3 was used (0 = none, 1 = minimal, 2 = moderate, 3 = marked). The mean of the grades of intensity was calculated from areas 1-4, 5-8, 9 and 10 (II).

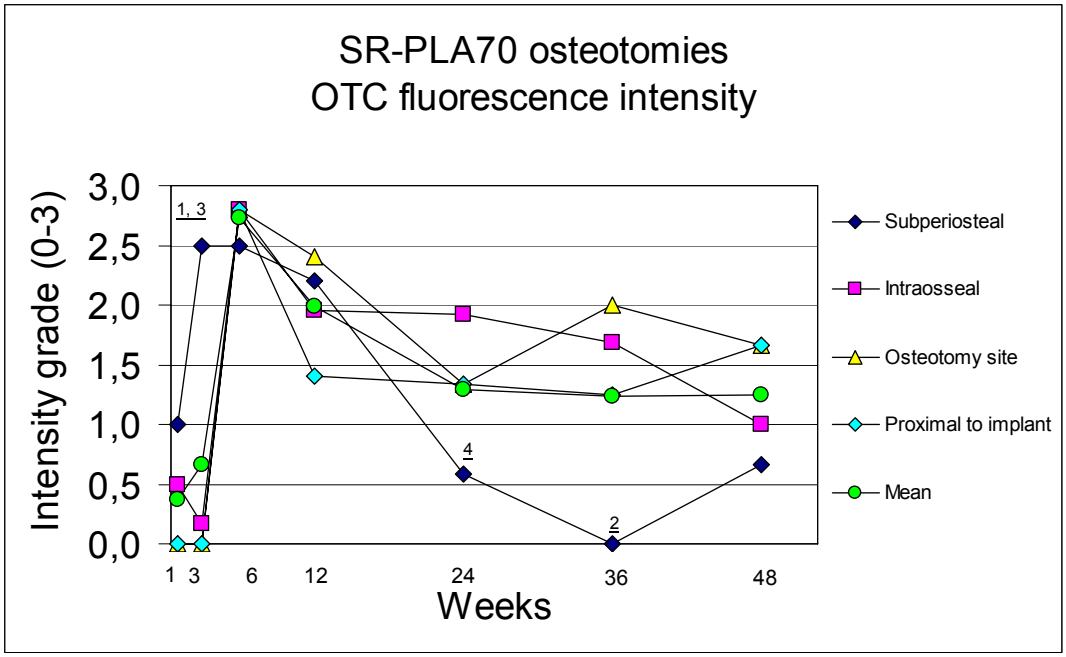


Figure 15. Oxytetracycline labelling results after fixation of the distal femoral osteotomies with SR-PLA70 rods. The mean of the grades of fluorescence intensity in different areas (0 = none, 1 = minimal, 2 = moderate, 3 = marked). Areas represent the intensities of subperiosteal region, intraosseous bone region near the implant, intraosseous bone near the osteotomy, and intraosseous bone proximal to the implant. From each area, the intensity of fluorescence was evaluated and a grading of 0-3 was used (0 = none, 1 = minimal, 2 = moderate, 3 = marked). 1 $p<0.001$ (Wilcoxon test with regard to other regions). 2 $p<0.000001$ (Wilcoxon test with regard to other regions), 3 $p<0.05$ ((Wilcoxon test with regard to 1 week specimens), 4 $p<0.0001$ (Wilcoxon test with regard to 12 weeks specimens) (I).

3.5. CLINICAL STUDIES

3.5.1. Patients and methods

The ethics committee of Mikkeli Central Hospital and Iisalmi District Hospital approved the plan of the present clinical studies. Each patient was informed of the new method and they provided informed consent for the study protocol. Randomization was carried out by using closed envelopes in the operating theatre.

3.5.1.1. Ankle fractures

Sixty-two adult patients with displaced ankle fracture needing operative treatment (unstable fracture, dislocation >2 mm and/or posterior tibial fracture fragment > ¼ of joint surface) were included in the study. Comminuted fractures needing plate fixation were excluded.
Thirty-two patients were operated on using SR-PLA70 and thirty patients using SR-PLLA screws. The mean age was 41 years (14-73). Thirty-eight patients were male. There were forty-four Weber B type and eighteen Weber C fractures. Twenty-four patients had a fracture of more than one malleolus.

3.5.1.2. Hallux valgus deformities

Thirty-two feet with symptomatic hallux valgus and metatarsus primus varus deformity were included in the study. Sixteen feet were randomized to SR-PLA70 and 16 to SR-PLLA screw groups.

Inclusion criteria to the study were (1) pain in the medial eminence of the first metatarsophalangeal joint (MTPJ), (2) hallux valgus (HV) and metatarsus primus varus deformity, (3) intermetatarsal angle (IMA) exceeding 10 degrees, (4) failure of conservative treatment (shoe modalities, pain management), and (5) signed informed consent. Exclusion criteria were (1) osteoarthrosis or (2) previous surgery of 1st MTPJ.

All patients were evaluated clinically preoperatively. The clinical evaluation included measuring the range of motion (ROM) of the first MTPJ. The passive ROM was measured with a goniometre. The stability of the 1st tarsometatarsal joint (TMTJ) was evaluated by holding the 1st TMTJ and medial cuneiform bone with one hand with the opposite hand grasping and moving the metatarsal head in a dorsal and plantar direction. Instability was defined as a movement exceeding 1 cm (Robinson and Limbers 2005). In addition, lack of heavy keratosis under the first ray was considered as a sign of unstable TMTJ.

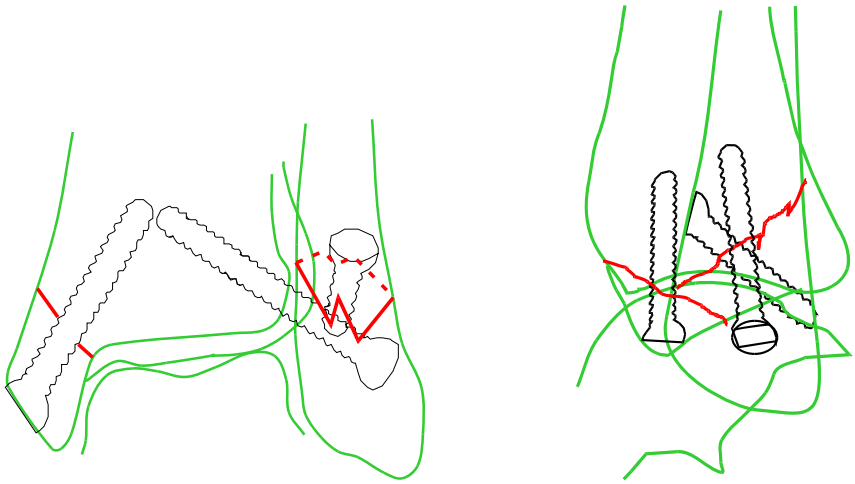
3.5.2. Operative techniques and postoperative treatment

3.5.2.1. Ankle fractures

Open reduction of the fracture was performed with clamps. After 3,2 mm drilling, tapping and countersinking with specialized instruments, one or more screws were inserted with a

special screwdriver. To maximize the grip of the screw, the lag screw technique was not used. If the lateral malleolus fracture line was short and one screw was not sufficient to stabilize the fixation, then either a 2 mm additional pin or a horizontal syndesmotic transfixation technique was used for the second screw (Figure 16). After the insertion of the screw, the excess part of the head was cut flush with an oscillating saw to the level of the cortical bone to avoid subcutaneous irritation. The wound was closed with mattress stitches.

A below-the-knee plaster cast was used for six weeks. During the first three weeks, ambulation did not incur any weight bearing, then there were two weeks with partial weight bearing and after five weeks, full weight bearing was allowed. Clinical and X-ray assessments were performed at three and six weeks and one year postoperatively.



A B

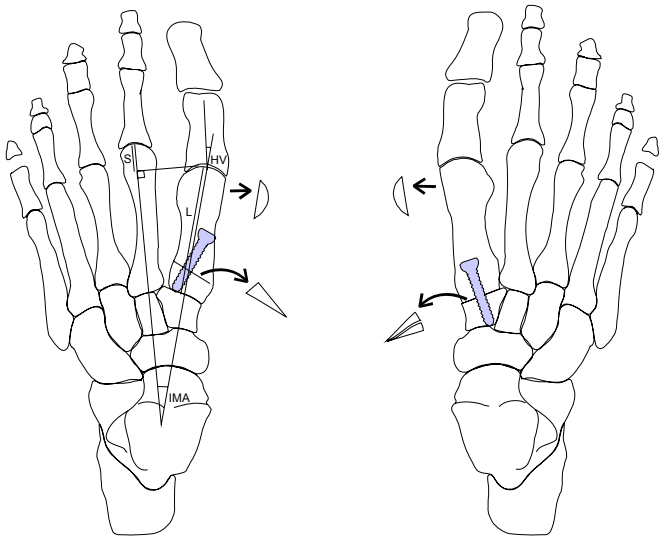
Figure 16. Schematic presentation of fixation method in a bimalleolar fracture. The lateral malleolus is fixed with one screw perpendicular to the fracture line. The second screw transfixes the syndesmosis through the distal fibula and tibia. The third screw fixes the medial malleolus. Screw heads are cut flush on the bone (III).

3.5.2.2. Hallux valgus deformities

The patients were treated using osteotomy of 1st MT bone or 1st TMTJ arthrodesis depending on the instability of 1st TMTJ evaluated under preoperative clinical examination.

Incision was made in the dorsomedial side of the 1st metatarsal bone. Distal soft tissues were released and medial eminence was excised. The adductor hallucis tendon was not dissected. The dorsomedial incision was extended proximally, the proximal metatarsal bone was exposed, and the periosteum was elevated.

Osteotomy (Figure 17 A): At 1 cm distal to the metatarsocuneiform joint, a laterally based wedge of bone was removed with an oscillating saw; care was taken to preserve the medial cortex to serve as a hinge in the osteotomy. The resulting osteotomy was closed and temporarily fixed with a clamp or K-wires. The osteotomy was then fixed with one or two bioabsorbable screws. To maximize the contact and the grip of the screw to the bone, the lag screw technique was not used. Usually the first screw was inserted from distal dorsal medial part towards the proximal plantar lateral side of the osteotomy. The screw was shortened with an oscillating saw to the level of the cortical bone to avoid subcutaneous irritation. The second screw was inserted from the distal medial part towards the proximal lateral part, if needed.



A B

Figure 17. (A) Proximal osteotomy of the 1st metatarsal bone. Schematic presentation of the operation technique and radiographic measures (hallux valgus (HV), intermetatarsal angle (IMA), length of the 1st metatarsal, shortening of the 1st metatarsal in direction of 2nd metatarsal). (B) Arthrodesis of the 1st tarsometatarsal joint. The joint was resected wedge like and fixed with one or two screws. The medial exostosis was resected (IV).

Arthrodesis (Figure 17 B): When the 1st TMTJ proved to be unstable, then arthrodesis was performed. The unstable TMT-joint was exposed and the articular surface was resected wedge-like laterally and in a plantarward direction with an oscillating saw to correct the metatarsus primus varus angle. The fixation was performed in a similar way as in the osteotomy patients. Usually the first screw was inserted from the proximal dorsomedial metatarsal bone towards the medial cuneiform bone in a plantarward direction and laterally.

To close the wound, the medial part of the capsule and the abductor hallucis tendon were plicated. Skin was closed with mattress stiches.

Postoperative treatment: A plantar plaster cast was used for six weeks. During the first three weeks, ambulation with touch bearing was allowed, followed by partial weight bearing for three weeks, and after six weeks full weight bearing was allowed.

3.5.3. Follow-up methods

3.5.3.1. Ankle fractures

Patients were followed up for one year with variables to be monitored as follows: age, sex, retirement, side of fracture, Weber classification (Weber and Colton 1991), number of fractured malleoli, duration of operation, sick leave, number of screws, patient subjective ratings, radiological findings and clinical result at one year, Olerud-Molander score (Olerud and Molander 1986) at one year, range of motion, radiological signs of syndesmotic ossification, radiological closing of the screw channel and incidence of complications.
The Olerud-Molander score evaluates pain, movement and stability of the ankle, and resumption of normal physical activities (stiffness, swelling, stair climbing, running, jumping, squatting, need for supports, work and activities of daily life). If the patient is suffering from pain or other complaints, then the score will be less than 100 points.

The patient subjective rating was enquired verbally during the office visits. The radiological result was assessed as good if the fracture had not dislocated, as moderate if the dislocation was less than 2 mm, and as poor if the dislocation was more than 2 mm. The clinical result was considered as good if there were no complications and the patient was able to use the ankle normally during ambulation, as moderate if there were minor problems during healing, and as poor if ambulation was restricted.

3.5.3.2. Hallux valgus deformities

The patients were interviewed and they were rated according to a standardized questionnaire based on the American Orthopaedic Foot and Ankle Society hallux-metatarsophalangeal-interphalangeal scale (HMIS) (Kitaoka et al. 1994). This scale assigns 40 points for pain, 45 points for function, and 15 points for alignment, with a possible maximum score of 100 points.

Overall patient satisfaction was assessed with a questionnaire at the final follow-up. The patients were asked whether the overall result of the surgery was good, moderate or poor.

All complications were noted. In particular, signs of infection, fluid accumulation (tissue reaction), thrombosis, breakage of the implant or poor reduction were noted.

Radiological measuring (Figure 17) was accomplished preoperatively and at the one year follow-up. Hallux valgus angle (HVA), IMA, shortening of the 1st metatarsal bone in a component of the 2nd metatarsal bone was measured and the change of these variables was calculated. Any possible enlargement of the implant channel was noted.

3.5.4. Statistical methods

The data were analyzed with SPSS software (SPSS Inc., Chicago, IL, USA). The distribution properties of the data were analyzed with Shapiro-Wilk test. Mann-Whitney U test was used for ordinal and nominal variables, and Fisher's exact test for two-grade variables. The non-parametric Mann-Whitney U test was used to compare variables. Statistical significance was determined as $p<0.05$.

3.5.5. Results of the clinical studies

A total of 87 patients were operated in the clinical studies. Seven patients in the hallux valgus deformity study underwent a bilateral operation.

3.5.5.1. Ankle fractures

Fifty-four out of sixty-two patients were followed up for one year. Eight patients (two in SR-PLA70 group and six in SR-PLLA group) were lost from the study: one died (suicide), and seven patients could not be contacted or did not want to participate in the one year evaluation.

In the comparison of the patients with the SR-PLA70 and SR-PLLA screws, sick leave time was the only statistically significant variable differing between the study groups (60 days in SR-PLA70 vs. 65 days in SR-PLLA, p=0,02). At the one year follow-up, the two study groups did not differ significantly in any of the measured variables. In the radiological evaluation, syndesmotic (ectopic) ossification was more common in SR-PLA70 group (5 patients) than in SR-PLLA group (1 patient), but this difference was not statistically significant. The other studied variables are presented in Table 9.

The screw channels were still visible radiologically in all patients at the one year follow-up.

Complications: There were no infections, nor any evidence of sinus formation or fluid accumulation in these patients. Forty-five patients were treated uneventfully. Seventeen patients experienced some complications with three being major problems which required reoperation (one residual displacement in the SR-PLLA group and one redisplacement patient in the SR-PLA70 group) or hospital care (one pulmonary embolism in the SR-PLLA group). Fourteen complications were considered as being minor but they are described in detail in the following paragraphs. There was no statistical difference in the incidence of complications between the study groups (8 in the SR-PLA70 and 6 in the SR-PLLA group).

Peroperative complications occurred in five patients (one major, four minor). One patient with trimalleolar fracture and malposition of the posterior trigonum needed a reoperation with a metal screw fixation. In four patients, there were minor difficulties in screw insertion (three screw breakages, one screw jamming). These did not affect the final results.

Twelve patients experienced postoperative complications (two major, ten minor). Four of these patients (two in SR-PLA70, two in SR-PLLA group) had more than a 2 mm redisplacement of the fracture: one needed a reoperation (reconstruction of the syndesmosis) and finally a talocrural arthrodesis 53 months postoperatively; the three other redisplacement patients did not need to be reoperated, and their final result was acceptable. Three of four patients with redisplaced fractures had risk factors: the first patient had an osteoporotic comminuted trimalleolar fracture, the second was a diabetic and the third had rheumatoid arthritis.

One patient (SR-PLA70) experienced a new trauma and a conservatively treated Weber B refracture eight months postoperatively. Recovery was uneventful and the patient reported no complaints at one year.

One patient with bimalleolar fracture (SR-PLLA) with delayed consolidation needed cast treatment for 13 weeks. The bone of this patient also had a fragile appearance resembling Sudeck atrophy, but consolidation was apparent at 13 weeks and there was an excellent final result at one year.

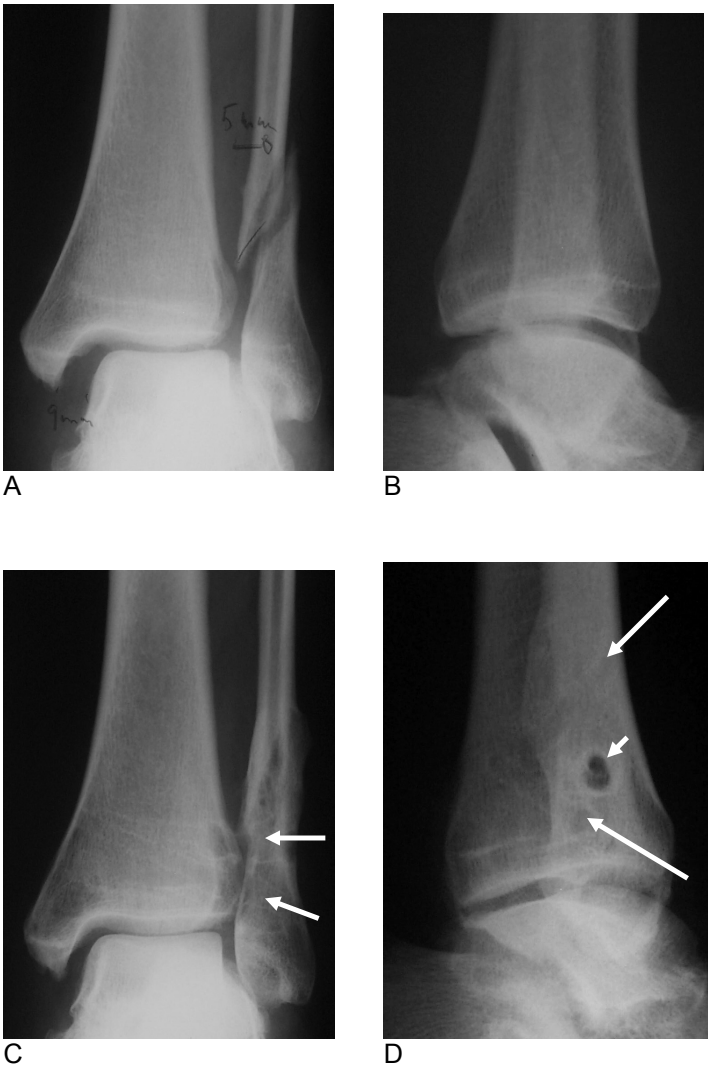
Six patients exhibited syndesmotic ossification at the one year follow-up (Figure 19). One of these patients had also a redisplacement and experienced discomfort during strenuous work or while taking long walks. The five other patients did not report any symptoms at the one year follow-up.

No adverse reaction (sinus formation) attributable to the bioabsorbable material could be detected in this series. However, two patients (one SR-PLA70 and one SR-PLLA) did report some itchiness in the operated region, though the skin and scar tissue of these patients appeared normal.

Table 9. Variables and results of the study groups in bioabsorbable fixation of ankle fractures in 62 patients (III).

	SR-PLA70	SR-PLLA	P-value
No. of patients	32	30	
Gender (male/female)	19/13	19/11	0.8
Age, years, median (range)	46 (14-69)	38.5 (17-73)	0.4
Retired	6	5	1.0
Weber-classification, B/C	24/8	20/10	0.6
Unimalleolar/polymalleolar fracture	20/12	18/12	1.0
Operating time, minutes, median (range)	53 (10-120)	50 (15-105)	0.8
Screws per operation, median (range)	2 (1-6)	2 (1-4)	0.1
Additional SR-PLLA pins used in operation, number of patients	4	5	1.0
Transfixation technique used in operation	3	6	0.8
Sick leave, days, median (range)	60 (38-195)	65 (58-152)	0.02
Range of motion after 1 year, median (range)	60° (45°-100°)	60° (45°-80°)	0.3
Subjective evaluation after 1 year, good/moderate/poor	25/4/0	18/6/0	1.0
Clinical evaluation after 1 year, good/moderate/poor	27/2/1	21/2/1	0.8
Radiological evaluation after 1 year, good/moderate/poor	26/3/1	21/2/1	1.0
Olerud-Molander score after 1 year, median (range)	100 (70-100)	97.5 (65-100)	0.3
Return to sports, yes/no	26/1	18/4	0.2
Syndesmotic ossification, yes/no	5/25	1/23	0.1

Figures 18 - 19. Radiographs of ankle fractures.



A B C D

Figure 18. Weber C type fracture. Preoperative (A, B) and one year postoperative (C, D) radiographs. Fixation with 3 SR-PLA70 screws. Talus is well reduced under the tibia. Note the bony callus of the fracture site. Screw channels are marked with arrows.

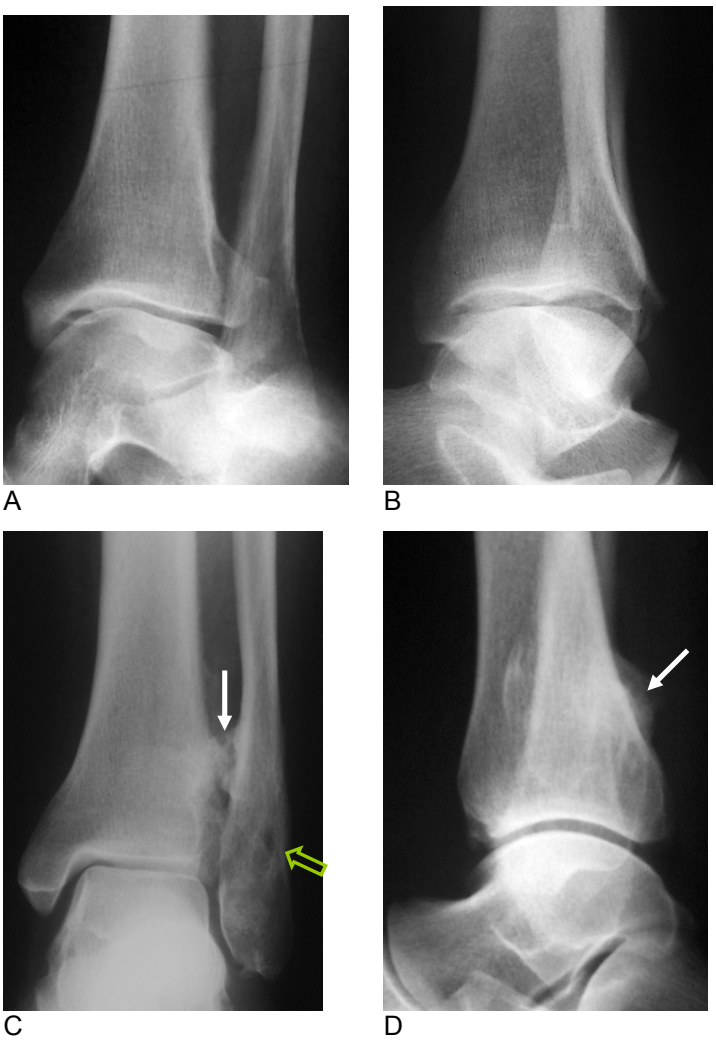


Figure 19. Weber B type fracture. Preoperative (A, B) and one year postoperative (C, D) radiographs. Malleolar fixation with one PLA70 screw. The screw channel is barely visible (open arrow). Note the syndesmotic ossification (white arrows) (III).

3.5.5.2. Hallux valgus deformities

In all, 25 patients with 32 feet were enrolled and randomized, with 16 feet in each group (SR-PLA70, SR-PLLA). Both feet were operated in 7 patients. No patients were excluded after enrolment to the study. All patients were followed up for 1 year. At the enrolment, the study groups were similar in terms of the patient characteristics.

26 feet in 20 patients were operated on using the osteotomy and 6 unstable 1st TMTJ feet in 5 patients were operated on using the arthrodesis.

Bony healing of 25 osteotomies and all (6) arthrodeses were seen at 6 weeks. One osteotomy in the SR-PLA70 group (patient 15, second operation) showed delayed consolidation and complete healing was seen at 26 weeks follow-up.
The mean IMA at 1 year follow-up was 11° (SD 4°) in SR-PLA70 group and 7° (SD 3°) in SR-PLLA group. The difference was statistically significant. The difference was not statistically significant, when the change of IMA was studied (p= 0.3).
The other studied variables are presented in Table 10.

No signs of implant breakage, fluid accumulation, tissue reactions related to bioabsorption of the implants, or enlargening of the implant channel were seen during the follow-up. Peroperative cleavage of the bone occurred in 5 operations. These were treated with additional pin fixation, except for one osteotomy (patient 8, first operation) in the SR-PLA70 group, in which the fixation of the osteotomy was considered adequate in spite of the fissure in the metatarsal bone. During the healing process, in this osteotomy loss of the correction was seen near to primary position so that the change of IMA was only 2° at 1 year.

Two superficial infections healed within 2-3 weeks with local therapy and peroral antibiotic. There were no thromboembolic complications.

Table 10. One year results of clinical, radiological and patient-reported outcome evaluation of 32 hallux valgus operations (IV).

	SR-PLA70 (n=16)	SR-PLLA (n=16)	Mean difference (95% CI)	p-value
Screws used per operation (one / two screws) [a]	15 / 1	13 / 3		0.6
Additional pins used per operation (0/1/2 pins) [e]	14 / 1 / 1	10 / 3 / 3	-0.4 (-0.9 to 0.1)	0.1
ROM, ° [b]	73 (7)	71 (12)	2 (-6 to 9)	0.7
Hallux valgus angle, ° [b]	19 (8)	17 (7)	2 (-4 to 7)	0.5
Hallux valgus angle change, ° [b]	16 (6)	16 (8)	0.3 (-5 to 5)	0.9
Intermetatarsal angle, ° [b]	11 (4)	7 (3)	3 (1 to 6)	0.01
Intermetatarsal angle change, ° [b]	8 (4)	9 (4)	-1 (-4 to 1)	0.3
1st metatarsal shortening related to 2nd MT, mm [b]	3 (4)	3 (3)	1 (-2 to 3)	0.3
1st metatarsal shortening related to 2nd MT change, mm [b]	3 (3)	2 (3)	1 (-1 to 3)	1.0
Any complication [a]	6	3		0.4
Peroperative cleavage of bone [a]	2	3		1.0
Superficial infection [a]	2	0		0.5
Retarded consolidation [a]	1	0		1.0
HMIS [b, c, d]	90 (11)	92 (9)	-2 (-10 to 5)	0.6
HMIS change [b, c, d]	36 (13)	37 (14)	0 (-10 to 10)	0.9
Overall patient satisfaction (good/moderate/poor) [d]	13/2/1	14/2/0		0.6

[a] Analysed by Fisher's exact test

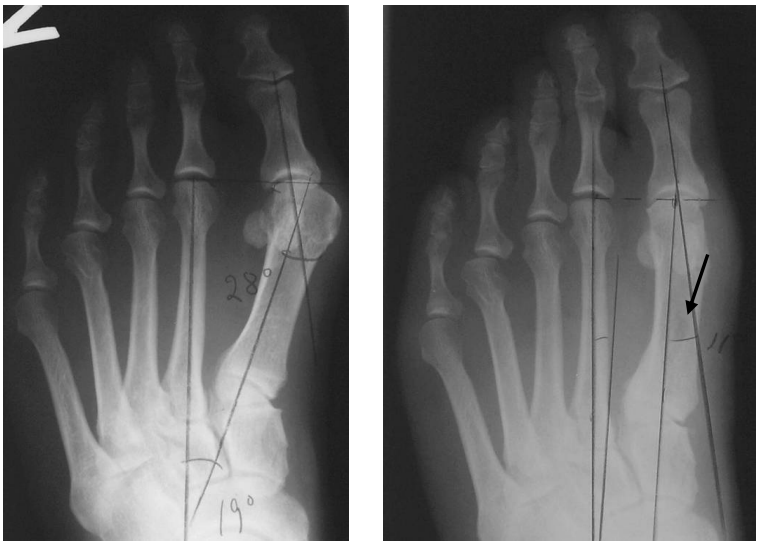
[b] Values are mean (standard deviation)

[c] Hallux-metatarso-interphalangeal score range 0 (most severe disability) to 100 (no disability)

[d] Mann-Whitney U analysis comparing the 2 groups

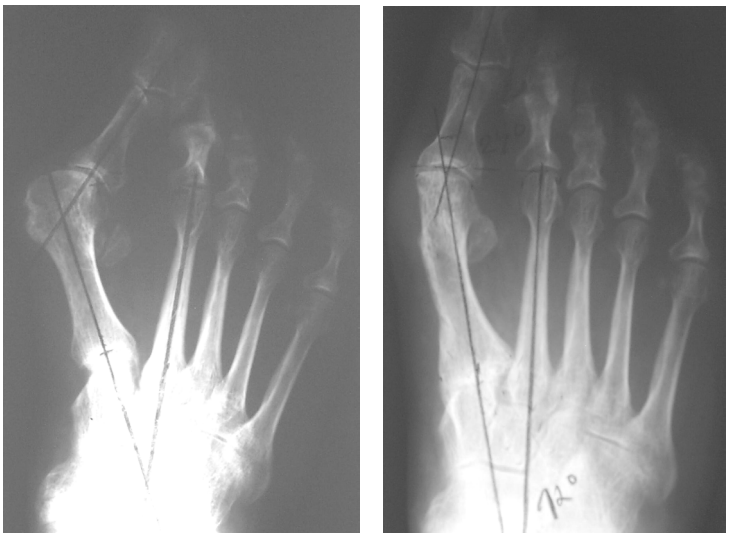
[e] Independent samples T-test

Figures 20 - 21. Radiographs of hallux valgus patients (IV).



A B

Figure 20. Proximal osteotomy, preoperative (A) and one year postoperative (B) radiographs (arrow = implant channel).



A B

Figure 21. First tarsometatarsal joint arthrodesis. Preoperative (A) and one year postoperative (B) radiographs.

4. GENERAL DISCUSSION

The present study is the first report to describe the use of drawn SR-PGA and SR-PLA70 implants in the fixation of experimental metaphyseal bone osteotomy and in clinical use in ankle fractures and proximal hallux valgus surgery.

Crystallinity

In the experimental studies (I and II), the crystallinity of the SR-PLA70 pins increased in vivo only slightly, and same was true with drawn SR-PGA pins. Since the foreign-body reactions of bioabsorbable implants can be a major problem, this is a highly desirable property (Ambrose and Clanton 2004, Bergsma et al. 1995a). In another study, non-reinforced PLA70 plates displayed increased crystallinity to 95 % at 60 weeks *in vitro* (Kellomäki et al. 2000) indicating that they would have a shorter degradation time of non-reinforced PLA70.

Initial strength

The SR-PLA70 implants in this study had an initial bending strength of 214 MPa, which is slightly less than the earlier results of SR-PLLA (Pohjonen et al. 1997, Törmälä et al. 1988) and SR-poly-L/DL-LA 92:8 (Saikku-Bäckström et al. 1999), but more than the strength of cortical bone. Pohjonen (Pohjonen and Törmälä 1997a) reported slightly weaker values (163 – 170 MPa) of SR-P(L/DL)LA70:30. In another study, SR-PLA70 pins possessed an initial bending strength of 192 MPa and shear strength of 125 MPa. Non-reinforced poly-L/DL-lactide 70:30 had also a weaker initial bending strength of 155 – 163 MPa (Claes et al. 1996).

Although SR-PLA70 is initially completely amorphous due to its high content of D-monomers in the polymer structure, it has been discovered that it is possible to self-reinforce not only to partially crystalline polymers, like PLLA or PLA96, but also to amorphous polymers (Pohjonen and Törmälä 1997b). The SR-structure of PLA70 is stronger than that of non-reinforced PLA70 and also the strength retention time is longer. On the other hand, the stereo-copolymer structure is more prone to hydrolytic degradation than homopolymer structure present in PLLA, leading to a faster degradation of the former structure.

The initial flexural strength of drawn SR-PGA pins was 270 MPa, which is slightly less than that found in earlier studies concerning SR-PGA manufactured with the sintering technique (Pohjonen et al. 1989, Törmälä 1992).

Strength retention and biodegradation

SR-PLLA implants retain their mechanical strength in hydrolytic conditions approximately three to ten times longer than the PGA-based implants (Saikku-Bäckström et al. 1999). Strength loss of PLA stereo-copolymers is usually faster than that of pure PLLA. The SR-PLA70 used in this study retained strength at the level of cortical bone (over 180 MPa) for over twelve weeks and still had flexural strength near 100 MPa (43%) at 52 weeks *in vivo*. The material used in this study has also been investigated earlier (Pohjonen and Törmälä 1997a): the present in vivo strength retention time was longer compared to in vitro results, though degradation in vivo proceeds usually at a faster rate (Pohjonen et al. 1997). Similarly, in another study concerning SR-PLA70, the strength properties had totally disappeared at 12 weeks in vivo. The molecular weight of SR-PLA70 in this study was initially 50800. The main reasons for this discrepancy is probably the fact the implant materials and the implants were not from the same batch, and there might have been some differences in their biodegradation rate (Hollinger and Battistone 1986). Several factors contribute to biodegradation of polymers in tissues and thus also to strength retention. Any quantitative evaluations should be done only in samples in which the physicochemical parameters (e.g. molecular weight, molecular weight distribution, monomer content, porosity, size of implant) are identical. Deficient characterization of these parameters in many studies complicates reliable comparison and explains the variation of strength retention values for the same polymer (Törmälä et al. 1998).

Non-reinforced P-L/DL-LA70:30 retained its mechanical strength in vitro at 36 weeks but had lost all of its strength at 72 weeks (Claes et al. 1996). In vivo, the same material was reported to lose strength completely in 3 months and degrade completely in 3 years (Gogolewski 2000).

In another study, concerning SR-PLLA rods, after 12 weeks *in vivo*, only 37 % (100 MPa) of the initial bending strength was present and there was no alteration in the shear strength. At the 36 weeks follow-up, the bending strength had decreased to the level of the strength of cancellous bone (10-20 MPa) and shear strength decreased slowly being 4,5

MPa at 48 weeks (Majola et al. 1992). In the study of Pohjonen et al. (1997) machine cut SR-PLLA screws lost their initial bending strength of 219 MPa slowly until nine weeks, after which the strength decreased more quickly, being 100 MPa at 26 weeks after the initial operation. The strength decreased in vivo faster than in vitro.

Saikku-Bäckström et al. (1999) measured the strength retention of SR-PLA96 and observed an excellent strength retention, lasting at least 24 weeks. Additionally, significant differences in strength retention could not be detected in *in vivo* or *in vitro* studies (Saikku-Bäckström et al. 1999).

In this study (I), histological analysis could not reveal any signs of biodegradation of SR-PLA70 pins in any specimens during the one year followup time, though in the SEM examination, the first signs of degradation in the form of microporosity of the implant were seen at 24 weeks *in vivo*, and the surface layer had peeled off and the self-reinforced structure was lost at 52 weeks. The same kind of histological result was observed also in another experimental study (Pyhältö et al. 2005).

In another study, non-reinforced P(L/DL)LA70:30 pins were used in the fixation of femoral condyle osteotomy of sheep. At 36 months, pins had microscopically disappeared and the channels were filled with bone or scar tissue (Prokop et al. 2005a).

The drawn SR-PGA pin lost its mechanical strength in 6 weeks (II). This is in accordance with earlier experimental animal studies concerning SR-PGA manufactured with sintering method (Böstman et al. 1991, Vainionpää et al. 1987, Vasenius et al. 1990). Manufacturing SR-PGA implants with the drawing method with a draw ratio of 3.0 produced a similar degradation rate compared to sintered SR-PGA implants.

Connective tissue and bone replaced the drawn SR-PGA implant channel solely in 36 weeks (II). Total degradation of the SR-PGA rod was observed histologically in 36 weeks also in another study (Nordström et al. 2001).

Healing of metaphyseal osteotomies

In the experimental studies (I and II), 56/70 (80%) osteotomies were firm. Altogether 12/77 specimens had to be excluded due to complications. This is considered to be an

acceptable level because of demanding operative procedure and the fact that the rats were allowed to use their limb freely after the osteotomy and single pin fixation.

Histomorphometric analysis showed that active osteoid formation reached its highest value at between 6 and 24 weeks in SR-PLA70 specimens and at 24 weeks in SR-PGA specimens.

OTC

In the OTC analysis, there were differences between the SR-PLA70 and SR-PGA materials: the SR-PGA specimens showed an increase in activity proximal to the implant at 24 weeks, which apparently was caused by degrading implant area inducing bone formation. The more slowly degrading SR-PLA70 retained a weaker osteostimulatory effect for a longer time.

Majola et al. studied SR-PLLA and SR-PLA80 (SR-PDLLA/PLLA 40:60) and observed high OTC uptake from one to three weeks, with a reduction noted at six weeks, from when no further OTC uptake was noticed. The reduction of uptake at six weeks was more appreciable with SR-PLA80 specimens. This is in concordance with the present study where OTC uptake remained for a longer period with the polymer containing more D-monomers, making this implant more prone to hydrolysis (Majola et al. 1991).

Nordström et al. (2002) osteotomized both femora, fixing one with an SR-PGA rod and the other with an SR-PLLA rod. They found the highest osteostimulatory effect in osteotomized rats' femur at 24 weeks after the fixation with the SR-PGA rod, and at 6 weeks after the fixation with the SR-PLLA rod. Their result with the SR-PGA is in concordance with our finding with drawn SR-PGA.

However, in a recent study SR-PGA, PDS, SR-PLLA and stainless steel pins were implanted without osteotomy under identical conditions in rabbit femora, but no statistically significant differences were found between the groups in the extent of the evoked osseous response. All implants caused a similar osteoconductive response in the cancellous bone surrounding the implant (Pihlajamäki et al. 2006).

The biocompatibility of SR-PLA70 (I) and SR-PGA (II) proved to be acceptable. There were no clinical signs of inflammatory reactions, i.e., fluctuant swelling, or sinus formation, or histologically manifest adverse inflammatory tissue reactions at the implantation site. This in concordance with other studies, where non-reinforced PLA70 pins did not elicit any clinically relevant inflammation reaction (Prokop et al. 2004, Prokop et al. 2005a). Also SR-PGA has proven to be well tolerated in earlier experimental studies (Böstman et al. 1992a, Pihlajamäki et al. 2006).

Clinical studies

Ankle fractures

In general, fixation with a metallic plate and several screws is the most common method used to fix a lateral malleolar fracture. Bioabsorbable malleolar fracture fixation has been demonstrated to be as good as a metallic plate and screw implants (Kankare et al. 1996). Simple metallic screw fixation of the lateral malleolus has also been evaluated (Hammacher et al. 1986), and there are published series with good results obtained with this material in lateral malleolus fractures (Tornetta and Creevy 2001). Kim reported three lateral malleolus dislocations in 70 patients treated with one or two metallic screws (Kim and Oh 1999). In our study, postoperative dislocation of the fracture occurred in four of 62 patients. This result is comparable to those of the other study (Kim and Oh 1999), which included Weber B fractures but not Weber C type fractures as in our study. In our series, three of four dislocation patients had risk factors, and these patients seemed to require a more stable fixation method than could be achieved with bioabsorbable screws alone. Bioabsorbable screw fixation can be used safely, when the patient does not have any risk factors and the bone quality is good.

No statistical difference between SR-PLA70 and SR-PLLA groups could be detected in clinical use and equal fixation strength was obtained perioperatively and during the healing time. The consumption of screws during the surgical procedure was the same in both study groups. The amount of screws used was at the same level also in another study, where 1.6 screws were applied for uni- and bimalleolar fractures, and 2.5 screws in severe ankle fractures, on average (Partio et al. 1992a). In our study, there was no difference in perioperative complications, these being related to the technique used with the implants. A screw 4.5 mm in diameter worked well for syndesmosis and medial malleolus fixation, whereas lateral malleolus could be fixed with smaller diameter screws as well. The screw

channel does require careful tapping to prevent unacceptable torque resistance during screw insertion. The strength of both SR-PLA70 and SR-PLLA screws was satisfactory in clinical use.

In the operations, some syndesmotic fixation screws of this study were implanted transsyndesmotically, i.e. obliquely through fibula and syndesmosis itself to tibia (Figure 16). This technique did not seem to have any negative effects on the clinical or radiological result. This is in accordance with another study where metallic syndesmosis screws were used (Kukreti et al. 2005).

Additional SR-PLLA pins were used if needed as extra fixation in some operations (four patients in SR-PLA70 vs. five in SR-PLLA). During the study, SR-PLA70 pins were not available. The influence of mixing the SR-PLLA pins in four operations of the SR-PLA70 screw group is considered to have had a negligible effect, because the need for additional pin fixation was equal in the study groups, the main fixation effect was achieved with the screws and the additional implant material was low in terms of volume.

There were no delayed wound healings or any infection cases in our study. In the large series of Sinisaari et al. (1996), the infection rate in 2073 ankle fracture patients with metallic implants was 4.1 %, compared with a rate of 3.2 % in patients operated on using bioabsorbable implants (p=0.3). One explanation for the low incidence of infections in our study may be related to the operative technique: there is a minimal need for soft tissue stripping and only a small amount of foreign implant material is used, when the lateral malleolar fracture is not plated. A similar result (no infection and no signs of skin necrosis) has been reported in other studies, where a simple metallic screw fixation was used in the osteosynthesis of ankle fractures (Kim and Oh 1999, McKenna et al. 2007, Tornetta and Creevy 2001).

In the follow-up, there was a statistical difference between the two ankle fracture groups only in one variable. The duration of sick leave was a few days shorter in the patients implanted with SR-PLA70 screws compared to those with SR-PLLA screws (60 days vs. 65 days, p=0.02). The patients were not, however, adjusted by profession, and thus the clinical importance of this finding is debatable.

Synostosis, a bony union between distal tibia and fibula, has been observed in 3.8 % - 6,5 % (Albers et al. 1996, Böstman 1993) of ankle fracture patients. Böstman (1993) claimed that synostosis existed only in ankle fracture patients treated with bioabsorbable SR-PGA rods, but not in metallic fixation patients, though Albers et al. (1996), reported a contrary finding when only metallic implants were used for malleolar fixation. In our study, the incidence of new bone formation (syndesmotic ossification) was quite common (11 % = 6/54). It is considered that ossification does not necessarily represent a rigid synostosis, but could also be a sign of ectopic callus formation in the area of syndesmosis associated with trauma and fracture healing *per se*. The patients with syndesmotic ossification were not subjected to a CT-scan. Furthermore, syndesmotic ossification seemed to be slightly more common when using the SR-PLA70 screw than the SR-PLLA screw (5 vs. 1), though the difference was not statistically significant (p=0.1). This phenomenon has not been found in earlier studies concerning SR-PLA70. However, in another study where SR-PGA was used, syndesmotic ossification was considered to represent an osteogenic potential of the bioabsorbable material (Böstman 1993), whereas a recent experimental report could not detect any difference in osteostimulatory or osteoinhibitory effects with PGA, PLLA, PDS or steel implant materials (Pihlajamäki et al. 2006). Theoretically, the faster biodegradation time or lower elastic modulus of SR-PLA70 compared to SR-PLLA could account for the slightly greater incidence of syndesmotic ossification incidence in SR-PLA70 patients. Further, syndesmosis ossification might theoretically be caused by syndesmotic transfixation screw fixation, but no such cases were observed in the nine patients who were operated on using this technique. In this study, the final functional and subjective result in syndesmotic ossification patients did not differ from the other patients, this being in concordance with the findings of previous studies (Albers et al. 1996). Additional reseach in the future will be needed to clarify the possible negative effect of syndesmotic ossifications, and the best method for imaging this potential problem is clearly computer tomography (Prokop et al. 2005b).

Hallux valgus

In the present study, bony healing and retention of corrected position of hallux was uneventful in all but two osteotomies; this result is comparable with that of another study in which metallic fixation was used (Trnka et al. 1999).

The basal closing wedge osteotomy of the first metatarsal bone has been used effectively to reduce the metatarsus primus varus component often associated with severe hallux valgus deformity, but in the case of an unstable TMTJ, arthrodesis of this joint should be performed (Hansen 2000, Robinson and Limbers 2005). In our series, 6 of the 32 feet (19 %) were treated with TMT-arthrodesis.

In the present study, additional SR-PLLA pin fixation was used in 8 patients due to an inadequate screw fixation. SR-PLA70 pins were not available for this study. The additional SR-PLLA material of the pins is considered to have only a minimal effect on the result of this study, because the main fixation was achieved with a screw and the pin material volume was relatively low compared to the screw material volume. In 5 out of 8 cases, additional pin fixation was needed due to bone cleavage. This is considered to be a consequence of the large size and mechanical stress of the 4.5 mm bioabsorbable screw. Meticulous countersinking of the screw head seemed to be of the utmost importance. In the other published studies, the smaller size 3.5 mm metallic or bioabsorbable screws have been used (Clare and Walling 2004, Hansen 2000, Trnka et al. 1999).

In the present study, no signs of tissue reaction or osteolysis related to bioabsorbance of the implants were seen. SR-PLLA implants rarely cause clinically detectable tissue reactions (Böstman and Pihlajamäki 2000a, b). Osteolytic changes have been described to exist with rapidly bioabsorbable polyglycolide implants (Pelto-Vasenius et al. 1997, Böstman and Pihlajamäki 2000b). The degradation rate of SR-PLA70 was seen to be slow enough and this evidently seemed to protect patients from clinically detectable tissue reactions. This finding is in accordance with an earlier clinical study concerning SR-PLA70 (Voutilainen et al. 2002).

In the present study, the mean HVA postoperatively did not differ statistically significantly in the study groups, but the mean IMA at 1 year was 4° less in the SR-PLLA group than in the SR-PLA70 group. The low incidence of implant failure and the delayed consolidation in both study groups is a sign of good fixation ability of both bioabsorbable screws. Additionally, the difference of the mean IMA in the study groups may not be clinically relevant, because the change of IMA was almost the same in the study groups.

The mean HVA at 1 year was 18°. This result is comparable with values reported by Trnka et al. (1999): (20°); Borton and Stephens (1994): (19°); and Anjum and Denolf (2006) (13°). HVA correction was 16° in our study, which is less than in the earlier studies (19°-24°) (Trnka et al. 1999, Borton and Stephens 1994, Anjum and Denolf 2006, Okuda et al. 2005). In all previous studies, the operative technique included an additional adductor tendon release, which was not used in our series. The IMA at one year follow-up in our study was 9°, which is slightly more than that in the series by Trnka et al. (1999), Borton and Stephens (1994), Anjum and Denolf (2006), and Okuda et al. (2005) (7°, 7°, 6° and 7°, respectively). Closing wedge osteotomy predisposes the 1st metatarsal bone to shortening of the 1st ray. Trnka et al. (1999) reported shortening of 5 mm. Comparison with our results is difficult, because Trnka et al. used a formula in their calculation. Our result of 3 mm of shortening is comparable to this result and acceptable with respect to the clinical result. As a matter of fact, the earlier study did not show correlation between shortening of the 1st metatarsal and patient satisfation (Trnka et al. 1999).

In the present study, HMIS and the patient satisfaction evaluation did not differ statistically significantly between the study groups. The results are comparable with other studies (Trnka et al. 1999: HMIS 89, 85 % of patients satisfied, Okuda et al. 2005: HMIS 92, 95 % of patients satisfied; Anjum and Denolf 2006: HMIS 89, 96 % of patients satisfied).

In conclusion, both SR-PLA70 and SR-PLLA screws proved to be equally safe in proximal metatarsal closing wedge osteotomies and TMTJ arthrodeses. The relatively large size of the 4.5 mm bioabsorbable screw may be a cause of perioperative bone cleavage complications. The one year follow-up time of this study is too short to clarify the possible difference in final biodegradation between SR-PLA and SR-PLLA screws. However, one year follow-up is long enough to show the differences in the perioperative and early postoperative complications, including the possible early tissue reactions. It is also clear that the clinical result of hallux valgus surgery is detectable after one year follow-up (Okuda et al. 2005, Veri et al. 2001), and the clinical results do not differ between 2 to five years (Trnka et al. 2000). A longer follow-up, up to eight years, would be needed to demonstrate any possible difference in the long-term clinical result and rates of degradation of SR-PLA70 and SR-PLLA screws.

5. CONCLUSIONS

On the basis of the present study, the following conclusions can be drawn:

1. The biocompatibility and fixation properties of the SR-P(L/DL)LA 70:30 pins are sufficient to fix the rat distal femur osteotomy.

2. The biocompatibilty and fixation properties of the drawn SR-PGA pins are sufficient to fix the rat distal femur osteotomy.

3. The SR-P(L/DL)LA 70:30 pins had an initial bending strength of 214.1 ± 4.2MPa and a shear strength of 120.9 ± 1.5MPa and after being implanted subcutaneously in rats for 52 weeks, the implants retained 43% of their bending strength and 41% of their shear strength. The drawn SR-PGA pins had an initial bending strength of 270 ± 30 MPa and a bending modulus of 13 ± 2 GPa and after being implanted subcutaneously in rats for 3 weeks, the implants retained 50 % of their bending strength and 46 % of their shear strength.

4. The SR-P(L/DL)LA 70:30 (SR-PLA70) and SR-PLLA screws are suitable for the fixation of selected cases of ankle fractures, if the bone quality is good and the mechanical stability of the fixation is perioperatively tested.

5. SR-PLA70 and SR-PLLA screws proved to be equally safe in proximal first metatarsal closing wedge osteotomies and tarsometatarsal arthrodeses.

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