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SELF-REINFORCED POLYGLYCOLIDE AND POLY-LEVO-LACTIDE PINS IN IMPLANTATION AND FIXATION OF OSTEOTOMIES IN CANCELLOUS BONE

An experimental study on rats

Pia Nordström

Academic dissertation

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To Tony, Emilia and Pii

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ABSTRACT

In the present study the tissue response was examined qualitatively and quantitatively to self-reinforced polyglycolic acid (SR-PGA) and self-reinforced poly-L-lactic acid (SR-PLLA) pins at cancellous bone either with or without osteotomy. The shear-load carrying capacities of cancellous bone implanted either with SR-PGA or SR-PLLA pins or after experimental osteotomy fixed either with SR-PGA or SR-PLLA pins were also investigated and compared with each other as well as with the unoperated femurs of rats during time function. In all studies the sizes of the implant were 2.0 mm in diameter and 15 mm in length. In two of the studies (*I, III)* the distal femurs were implanted with an SR-PGA pin in one hind leg and with an SR-PLLA pin in the other hind leg of the same rat. In the two other studies *(II, IV)* the pins were fixed in the same way, but transversal osteotomies were done in the distal femurs. The follow-up periods were one, three six, 12, 24, 36, 48, and 52 weeks.

The biocompatibility of both polyglycolide and polylactide proved to be good. The tissue reaction to the implant was examined radiographically, histologically, histomorphometrically, microradiographically, and using oxytetracycline fluorescence studies. In the histomorphometric studies the follow-up groups consisted of five operated rats. The intact femurs of eight non-operated rats were used as controls. In an experimental study of 51 rats *(I)*, in which the pins were implanted in the distal part of intact femurs, active new bone formation was seen close to the implant surface at one week in both groups. At 12 weeks the mean fractional osteoid formation surface was significantly ($p < 0.01$) higher in the SR-PGA-implanted specimens compared with the SR-PLLA-implanted specimens. At that time there were also significantly ($p < 0.05$) more phagocyting macrophages in the SR-PGA-implanted specimens than in the SR-PLLA-implanted specimens, which is in accordance with the degradation behaviour of both implants. The first signs of degradation of the SR-PGA pin were seen at three weeks, and the pin was totally degraded by 36 weeks. No signs of degradation of the SR-PLLA pin were observed during the follow-up period. In an experimental study of 49 rats *(II)*, in which the pins fixed the osteotomized cancellous bones, a vigorous osteostimulatory tissue response, indicated as the number of osteoblasts over the total trabecular surface, to the SR-PGA pin and the SR-PLLA pin was observed at one week after fixation. This reaction reached its highest value 24 weeks after SR-PGA and six weeks after SR-PLLA pin fixation. The greatest values of the mean trabecular bone area fraction, 27.9 % for SR-PGA and 28.1 % for SR-PLLA pins, were measured at 48 weeks. At 12 weeks there was a peak number of phagocytizing macrophages in the specimens with SR-PGA pin fixation. Total phagocytosis of SR-PGA implants was seen, but few signs of degradation of SR-PLLA pins were observed.

The shear-load carrying capacities of the distal femurs of 40 rats were investigated *(III)*. In the study SR-PGA and SR-PLLA were implanted in both femurs of the same animals, as the intact femurs of 20 rats served as controls. The shear-load carrying capacities reached their highest values at 36 weeks both in the SR-PGA- and SR-PLLA-implanted specimens and also in the control bones. After that they gradually decreased, and at 52 weeks both the SR-PGA-implanted specimens and the control bones had significantly ($p < 0.001$) higher values than the SR-PLLA-implanted specimens. Otherwise the values were higher in the SR-PLLA-implanted specimens. The mean shear-load carrying capacity of the SR-PGA-implanted specimens was 171 N and that of the SR-PLLA-implanted specimens 181 N, the value of the control bones being 148 N. In an experimental study of 40 rats *(IV)*, in which osteotomized distal femurs were fixed either with SR-PGA or SR-PLLA pins, the shear-load carrying capacities reached their highest values at 24 weeks in the SR-PGA-fixed specimens. After that the values decreased. In the SR-PLLA-fixed specimens the shear strength values of the pins decreased after 12 weeks. There was a decrease at 24 weeks and after that the shear-load carrying capacities started to rise. At the end of the 52-week follow-up time both the SR-PGA and SR-PLLA-fixed specimens had significantly ($p < 0.001$) higher values compared to the control specimens. Thus, in the control specimens the shear-load carrying capacities were weaker than in the SR-PGA- and SR-PLLA-fixed specimens except at three weeks, as the osteotomies had not yet healed, but the shear strength values of the pins were no more as high as at the beginning. During the whole follow-up period the mean shear-load carrying capacitiy of the SR-PGA-fixed specimens was 199 N and that of the SR-PLLA-fixed specimens 215 N, whereas the corresponding value of the control specimens was 148 N.

LIST OF ORIGINAL PUBLICATIONS

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

I Nordström P, Pihlajamäki H, Toivonen T, Törmälä P, Rokkanen P. Tissue response to polyglycolide and polylactide pins in cancellous bone. Arch Orthop Trauma Surg 117:197-204, 1998

II Nordström P, Pihlajamäki H, Toivonen T, Törmälä P, Rokkanen P. Tissue response to polyglycolide and polylevolactide pins in osteotomized cancellous bone. Clin Orthop 382:247-257, 2001

III Nordström P, Pohjonen T, Törmälä P, Rokkanen P. Shear-load carrying capacity of cancellous bone after implantation of self-reinforced polyglycolic and poly-L-lactic acid pins. Experimental study on rats. Biomaterials *(in press)*

IV Nordström P, Pohjonen T, Törmälä P, Rokkanen P. Shear-load carrying capacities of the distal rat femurs after osteotomy fixed with self-reinforced polyglycolic acid and poly-L-lactic acid pins. J Mater Sci: Mater Med *(in press)*

LIST OF ABBREVIATIONS

Acetyl-CoA	acetyl co-enzyme A
ACL	anterior crucial ligament
ANOVA	analysis of variance
ß	beta
C	carbon
°C	Celcius
CA	California
cm	centimetre
F	force
g	gramme
G-C	giant cell
GPa	giga Pascal (10^9 N/m^2)
h	hour
H	hydrogen
HSD	honestly significant differences
i.e.	*id est* = that is
i.ex.	for example (e.g. = exempli gratia)
IU	international unit
kg	kilogramme
kV	kilo Volt
µm	micrometre
mAs	milli Amper second
M-F	macrophage
mg	milligramme
mm	millimetre
min.	minute
MPa	mega Pascal (10^6 N/m^2)

Mrad	mega rad (10^6 rad)
M_v	viscosity average molecular weight (g/mol)
N	newton
n	number
O	oxygen
OR	Oreganon
OTC	oxytetracycline
PDLA	poly-D-lactic acid or poly-D-lactide
PDLLA	poly-DL-lactic acid or poly-DL-lactide
PDS	polydioxanone
PGA	polyglycolic acid or polyglycolide
PLA	polylactic acid or polylactide
PLLA 96	poly-96L/4D-lactic acid or poly-96L/4D-lactide
PLLA	poly-L-lactic acid or poly-L-lactide
r.t.	room temperature
s.c.	subcutaneous
SR	self-reinforced
T_g	glass transition temperature (°C)
T_m	melting temperature (°C)

1. INTRODUCTION

The ideal osteosynthesis of fractures or osteotomies is that the fixation is sufficient during the time of healing and that after healing the osteosynthesis implant has resorbed and there is no need to remove it.

The use of bioabsorbable implants made of polyglycolide/polylactide (Rokkanen et al. 1985, Böstman et al. 1987), polyglycolide (Becker 1988, Böstman et al. 1989b, Hoffmann et al. 1989, Leixnering et al. 1989, Hirvensalo et al. 1990, Kristensen et al. 1990, Ruf et al. 1990, Hope et al. 1991, Kumta et al. 1992, Dijkema et al. 1993, Ahl et al. 1994, Svensson et al. 1994), and polylactide (Partio et al. 1992c, 1992d, Nakamura et al. 1993, Niskanen et al. 1993, Pihlajamäki et al. 1994e, Rehm et al. 1994, Juutilainen and Pätiälä 1995) in orthopaedics and traumatology is nowadays widely accepted. The areas of use of these polymers have been increasing with time because of some unique attributes of these polymers. These polymers have to be totally bioabsorbable, but they have to retain their functionality for a given period of time. Furthermore, their degradation products have to be non-toxic and biocompatible. Raw materials from different sources often differ considerably in their physicochemical characteristics (Kulkarni et al. 1971, Hollinger and Battistone 1986, Böstman 1991a, Majola et al. 1992a, Manninen 1993b, Bucholz et al. 1994, Böstman et al. 1995), which may affect the biocompatibility of the implants manufactured.

Foreign-body reactions have been mentioned in connection with bioabsorbable fixation devices; these reactions obviously represent an inherent biologic tissue response to the degradation and absorption processes of these materials (Böstman et al. 1990a, Santavirta et al. 1990, Böstman 1991b, Miketa and Prigoff 1994, Frederick et al. 1996, Hovis and Bucholz 1997). Also synovitis is said to be a conspicuous clinical feature of an acute tissue reaction to bioabsorbable implants (Böstman et al. 1990a, Hirvensalo et al. 1990, Barfod and Svendsen 1992, Böstman 1992, Fridén and Rydholm 1992, Lavery et al. 1994, Pelto-Vasenius et al. 1995, Hovis and Bucholz 1997).

In addition to the basic requirements, bioabsorbable fixation devices have to show a certain level of mechanical properties before implantation and they have to retain a required level of mechanical properties after their implantation during the healing of fixed tissues. The mechanical properties of degradable implant materials are low in comparison to metals used in orthopaedic surgery. There are possibilities to improve the strength of degradable implants by self-fibre-reinforcement, high molecular weight or special manufacturing processes. However, the moduli of the materials cannot be increased significantly with these techniques (Claes 1992).

Törmälä et al. (1986) published the first definition of the ultra-high-strength self-reinforced (SR-) totally biodegradable osteosynthesis materials. SR-materials and devices, which are based on polyglycolides, polylactides, and their copolymers, have, so far, been studied most profoundly (Vainionpää et al. 1989, Partio et al. 1996, Pelto-Vasenius et al. 1996a, 1996b, Rokkanen et al. 1996) .

The present study deals with tissue responses and shear-load carrying capacities of both SR-PGA and SR-PLLA-fixed bones with or without osteotomy on rats. It is essential to know which implant to choose for different fractures and osteotomies. Also, the use of absorbable implants saves costs, as it releases resources of operative capacity for other operative purposes due to no need of a secondary operation.

2. REVIEW OF THE LITERATURE

Poly-alpha-hydroxy acids constitute a particular class of polymers which are derived from alpha-hydroxy acids. This class has been under research for the development of osteosynthesis devices since the 1960s (Kulkarni et al. 1966, Schmitt and Polistina 1969, Cutright and Hunsuck 1972, Vert et al. 1981, Vainionpää 1986, Vihtonen et al. 1987). Implants made of polyglycolic acid (PGA) or polylactic acid (PLA) are the strongest to be developed from this class (Vert et al. 1981).

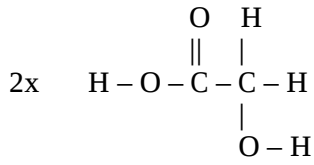
2.1. POLYGLYCOLIC ACID

2.1.1. Chemistry

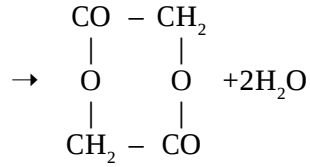
Polyglycolic acid (PGA) with a low molecular weight was synthesized by Bischoff and Walden in 1893, whereas high-molecular-weight PGA with plastic properties was introduced by Higgins in 1954. Polyglycolic acid with a high molecular weight is a hard, tough, crystalline polymer melting at approximately 224-228 °C with a glass transition temperature (T_g) of 36 °C (Frazza and Schmitt 1971, Vert et al. 1986, Törmälä et al. 1998). PGA is insoluble in most of the common polymer solvents. It is more polar than several other aliphatic polyesters and therefore quite hydrophilic. The molecular weight of a polymer to spin into a fibre form is, on average, 20 000 - 145 000 (Frazza and Schmitt 1971). PGA can also be spun into films and different kinds of objects like pins, rods, plates and screws (Schmitt and Polistina 1969, Gilding and Reed 1979, Vainionpää et al. 1989).

2.1.2. Synthesis

Glycolic acid or hydroxyacetic acid is a monomer forming a cyclic diester, glycolide, by dehydrating:



Glycolic acid



Glycolide

Polyglycolic acid (PGA) or polyglycolide can be synthetized 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

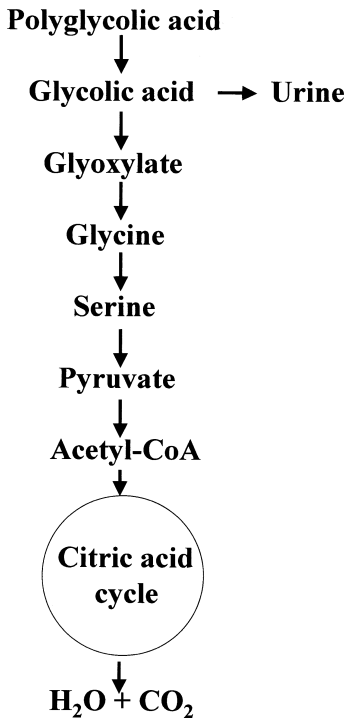


Figure 1. Biodegradation of polyglycolide (Frazza and Schmitt 1971, Williams 1982, Hollinger 1983, Hollinger and Battistone 1986).

2.1.3. Biodegradation

The biodegradation of PGA goes through hydrolyzation in aqueous environment by essentially the same mechanism *in vivo* and *in vitro*, but the enzymatic activity enhances the degradation process *in vivo* (Williams 1979, 1982). The hydrolytic degradation *in vivo* may take place by non-specific esterases and carboxyl peptidases that produce glycolic acid monomers which are converted enzymatically into glycine which can be used in protein synthesis or into pyruvate which can be emphased in mitochondrial energy production. Thus, the final products are mainly carbon dioxide and water, though the glycolic acid is partially extreted in urine (Frazza and Schmitt 1971, Williams 1982, Hollinger 1983, Hollinger and Battistone 1986) (Fig. 1).

The degradation time varies depending on variable tissue environment, the molecular weight, the purity and crystallinity of the PGA, as well as on the size and shape of the implant (Miller et al. 1977, Vainionpää et al. 1989, Törmälä et al. 1990) The large size of the implants and the high molecular weight delay the degradation (Hollinger and Battistone 1986, Törmälä et al. 1991).

The degradation time is faster in bone than in subcutaneous tissue (Vasenius et al. 1990a). Vainionpää (1986) found that PGA implants degrade to a great extent in cancellous bone and partly in cortical bone of rabbits within 12 weeks, with degradation starting from periphery inwards. The degradation of PGA cylinders in the sheep femurs occurred in four to five months (Christel et al. 1982), while PGA screws in the rabbit distal femurs disappeared in nine months (Böstman et al. 1992b) or had not degraded within nine months when PGA cylinders were implanted in the tibial cortices of rats (Vert et al. 1984).

2.1.4. Biocompatibility

2.1.4.1. Experimental studies

PGA as a suture material is well tolerated by soft tissue, evoking only a minimal inflammatory response (Hermann et al. 1970, Craig et al. 1975). In the first experimental studies PGA was biocompatible in bone tissue with no signs of inflammatory or foreign-body reaction (Vainionpää 1986). Miller et al. (1977) found that PGA is metabolised entirely without any vital organ accumulation. Moderate transient foreign-body reaction to SR-PGA screws in the rabbit cancellous bone was seen histologically by Böstman et al. (1992d) and by Vasenius et al. (1990b) and to SR-PGA membranes implanted in the back muscles of rabbits by Puumanen et al. (1995).

PGA screws studied in the rabbit cancellous bone showed a regular front of phagocytes around the implants (Böstman et al. 1992a), being highest at 12 weeks. Päivärinta

et al. (1993) found that foreign-body reaction with giant cells adhering to the implant surface was at maximum at three to six weeks, whereas macrophages and scanty numbers of polymorphonuclear round cells were at maximum at 12 weeks.

The fixation properties of PGA sutures (Vihtonen et al. 1987), rods (Vainionpää et al. 1986, Axelson et al. 1988), and screws (Vasenius et al. 1994) have proved to be sufficient for experimental conditions, such as fractures of cancellous bone, and also for fixation of diaphyseal femoral osteotomy using intramedullary implants in growing dogs (Miettinen et al. 1992). Studies on SR-PGA membranes to repair bone defects have been reported in rats and rabbits, and these devices have been found biocompatible and applicable in the treatment of bone defects and osteotomy augmentation (Ashammakhi et al. 1994a, 1994b, 1995a, 1995b, 1995c, Ashammakhi 1996). SR-PGA membranes can be used as a scaffold to obtain pre-designed rectangular bone from free tibial periosteal grafts in growing rabbits (Puumanen et al. 2000).

During degradation of the polymer increased osmotic pressure develops in the implant channel leading to transient osteolytic expansion of the implant cavity (Böstman et al. 1992b), transient osteolysis (Böstman et al. 1991), and increase in the diameter of the implant channel in the bone (Böstman 1992); also dispersion and migration of PGA particles from the implant cavity to cancellous marrow spaces, up to 2.8 mm, have been recorded (Böstman et al. 1992a).

Weiler et al. (1996) studied the effect of PGA rods in 12 sheep with standardised osteochondral fractures of the medial condyle fixed with uncoloured, self-reinforced PGA rods (Biofix®), and eleven of the 12 fractures healed radiographically and histologically. Moderate to severe osteolysis was seen at four to six weeks after maximal changes at 12 weeks in ten animals.

2.1.4.2. Clinical studies

The first series of fixations of ankle fractures with absorbable rods was reported by Rokkanen et al. (1985). After successful experiences of the clinical use of absorbable rods (Böstman et al. 1987, Hirvensalo et al. 1990, Rokkanen 1990, 1991), fixation of fractures, osteotomies, and arthrodesis was started at the Department of Orthopaedics and Traumatology, Helsinki University Central Hospital. Hirvensalo (1990) and Hirvensalo et al. (1990, 1991) obtained results with SR-PGA rods which were comparable with those obtained with metallic-fixed ankle fractures, radial head fractures, and chevron osteotomies.

SR-PGA rods (Hoffmann et al. 1989, 1992) and PDS-coated PGA rods (Casteleyn et al. 1992) have been used in the treatment of displaced fractures of the distal radius with good functional results. SR-PGA pins (Pelto et al. 1994) and PDS-coated PGA pins (Hirvensalo et al. 1990) have shown good fixation properties in the treatment of radial head fractures. Also the results of the studies of elbow fractures of children treated with SR-PGA pins have been satisfactory (Böstman et al. 1989b, Hope et al. 1991, Mäkelä et al. 1992, Svensson et al. 1994). Olecranon fractures have been fixed successfully with SR-PGA pins or screws (Partio et al. 1992b). Fractures of the medial humeral epicondyles treated with SR-PGA screws and rods in 21 patients (Partio et al. 1996) and humeral capitellum fractures treated with SR-PGA pins in eight patients have yielded favourable results (Hirvensalo et al. 1993).

Rokkanen et al. (1985) published the preliminary clinical study using PGA/PLA rods and sutures and metallic implants in the treatment of displaced uni- or bilateral malleolar fractures in 44 patients with good results. After that several prospective studies with satisfactory functional and radiographic results have been reported in displaced unimalleolar (Leixnering et al. 1989), bimalleolar (Böstman et al. 1990b), and severe ankle fractures (Hirvensalo 1989). Partio et al. (1992a)

studied 152 patients, in which favourable results were obtained in 93 % of the fixed uni- or bimalleolar fractures and in 81 % of the fixed severe ankle fractures.

In studies of cancellous bone absorbable polyglycolide seemed to be a suitable fixation material. Kankare (1997) studied six patients with a displaced split-depression-type tibial condylar fracture which were operated using SR-PGA screws with good functional and anatomical results despite one slight redisplacement. Another six patients with a displaced fracture of the neck or body of the talus were treated with SR-PGA screws and rods with no re-displacements (Kankare and Rokkanen 1998). This proves that biodegradable implants have sufficient stability to be used in the fixation of fractures of weight-bearing cancellous bone. In a prospective study 25 displaced intra-articular fractures of the calcaneus were treated operatively with absorbable SR-PGA rods. The results were similar to those with metallic implants; thus the use of SR-PGA rods is a potential addition to the treatment of these fractures (Kankare 1998).

In a prospective randomized study of 37 patients more than 65 years of age, Kankare et al. (1996) found no difference in the stability of fixation between SR-PGA-treated and metallic-treated malleolar fractures, whereas in a study of 16 alcoholics the results were poor because of their unwillingness to co-operate (Kankare et al. 1995).

The transient inflammatory reactions have manifested as non-bacterial fluid accumulation or sinus formation in 4.5 % of the non-coloured and in 18 % of the first generation SR-PGA screws with aromatic quinone dye (Böstman et al. 1992c). Similar reactions were also seen in 7 - 8 % of malleolar fractures (Böstman et al. 1987), ankle fractures (Hirvensalo 1989), and displaced fractures of the radial head (Hirvensalo et al. 1990). In delayed union and non-united fractures of the carpal scaphoid these reactions appeared in 25 % of the fixations (Pelto-Vasenius et al. 1995). Osteolytic changes were found after polyglycolide pin fixation in displaced ankle fractures (Frokjaer and Moller 1992) and in chevron osteotomies in 22 % of the studied cases (Pelto-Vasenius et al. 1997). Sinisaari et al. (1996) found that in displaced ankle fractures the infection rate was 4.1 % with metallic fixation compared to 3.2 % with absorbable fixation. Immunological studies revealed only a slight non-specific lymphocyte activation secondary to inflammatory mononuclear cell migration and adhesion (Santavirta et al. 1990).

Böstman and Pihlajamäki (2000) found among 2037 patients operated on by using pins, rods, bolts, and screws that 5.3. % of the devices made of polyglycolic acid were affected by clinically significant local inflammatory, sterile tissue reaction. The histopathologic picture was that of a non-specific foreign-body reaction.

2.1.5. Mechanical properties

The first poly-alpha-hydroxy acid, which was developed as sutures, was made of PGA. It was commercially available since 1970 as Dexon® sutures (Gilding and Reed 1979). The mechanical properties of PGA sutures were studied by Hermann et al. (1970). They measured a tensile load-carrying capacity of 40 N and an initial tensile strength of 980 MPa for 3-0 size threads. Frazza and Schmitt (1971) showed that the implantation of PGA threads subcutaneously in rabbits decreased the tensile strength to 50 per cent of the original value at one week. Reed and Gilding (1981) noticed that 80 per cent of the initial tensile strength of PGA sutures was maintained in aqueous environment for two weeks *in vitro*, but after four weeks most of the strength was lost. Williams (1979) presented the faster decrease in mechanical strength of PGA sutures *in vivo* than *in vitro*. This may indicate the significant role of enzymatic activity in the hydrolysis of PGA.

Absorbable osteosynthesis implants can be manufactured in several ways, for example by compression moulding and injection

moulding if moderately strong implants are needed (Vert et al. 1981). The self-reinforcing technique (SR) introduced by Törmälä et al. (1986, 1988) has enabled the manufacturing of these implants with sufficient strength. In this method, fibres of PGA are sintered together at a high temperature and pressure leading to 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 much higher than that of absorbable implants manufactured by any other method (Törmälä et al. 1988, 1990, 1991, Törmälä 1992).

There have been several experimental animal (Vainionpää 1986, Vasenius et al. 1989, 1990a, Böstman et al. 1991) and clinical studies (Böstman et al. 1987, 1989a, 1989b, Hirvensalo 1989, Hirvensalo et al. 1990) showing that SR-PGA has sufficient fixation properties for fixation of cancellous bone fragments. As these implants are the most hydrophilic absorbable polymers, they also lose their tissue-supporting properties too rapidly within the fracture healing time of cortical bone, though their initial mechanical strength is higher than that with SR-PLLA (Vainionpää et al. 1989, Vasenius et al. 1989).

The shear strength of the rod decreases to the level of cancellous bone in four to six weeks in the subcutis of the rabbit (Pohjonen et al. 1989, Vasenius et al. 1989). In one study Vasenius et al. (1990a) showed that the loss rate of the bending and shear strength of SR-PGA rods was significantly higher in the subcutaneous tissue and in the medullar cavity than in the distilled water at 37 °C. There was no significant difference between the loss of mechanical strength of the rods between the medullar cavity and the subcutis, as the rate of mechanical loss in the medullar cavity was only slightly higher than in the subcutis. On the contrary, the SR-PGA membranes lost their strength faster *in vitro* than *in vivo*, by six weeks, but they retained their strength for 15 weeks *in vivo*, due to the fibrous tissue that formed around and inside the implant (Ashammakhi et al. 1995a).

Encouraging results of SR-PGA screws in the treatment of fractures of the distal femoral epiphyses in adolescents have been published (Partio et al. 1997).

2.2. POLYLACTIC ACID

2.2.1. Chemistry

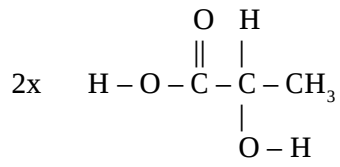
A high-molecular-weight polylactic acid (PLA) with plastic properties was introduced by Schneider in 1955. Polylactic acid is a hard, pale-coloured, semi-crystalline polymer with thermoplastic properties.

The lactic acid is asymmetric. Thus, polylactic acid exists in two enantiomeric forms, poly-L-lactic acid (PLLA) and poly-D-lactic acid (PDLA). They are two optically active stereoisomers with similar intrinsic chemical properties but opposite configurational structures (Cutright et al. 1974, Vert et al. 1984). The physical and chemical properties of the copolymers of L-lactic acid (PLLA) and D-lactic acid (PDLA) are dependent on the relative amounts of L- and D-monomers in the polymer chain. PLA has four different compound forms depending on the L- and D-configuration of the lactic moieties forming the molecules (Holten and Rehbinder 1971, Vert et al. 1981, Eling et al. 1982).

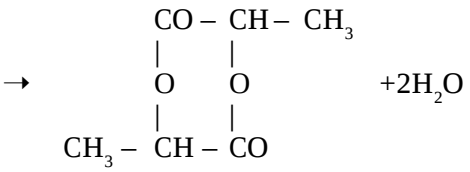
A highly crystalline polymer PLLA has a melting temperature (T_m) of 174-184 °C and a glass transition temperature (T_g) of 57-58 °C, when the molecular weight is over 100 000 (Vert et al. 1981, Jamshidi 1984, Hollinger and Battistone 1986, Törmälä et al. 1998). PLLA is hydrophopic because of the methyl group, causing quite a slow invasion of water molecules between the PLLA chains and crystals. Racemic poly-DL-lactide (PDLLA) does not form crystals like PLLA, resulting in weaker and more rapidly degradating implants (Kulkarni et al. 1971, Vert et al. 1981, Majola et al. 1991).

2.2.2. Synthesis

Polylactic acid can be produced by linear condensation polymerization as described by Higgins in (1954). A more efficient method to produce a high-molecular-weight polymer (Schneider 1955, Jamshidi 1984) is by anionic ring opening polymerization of cyclic diesters of lactic acid, under the influence of a low catalyst (inorganic metal salt) concentration as described by Lowe in (1954):



L-lactic acid



L-lactide

For the resultant polymer the following formula is commonly used:

$$[CH(CH_3)CO - O - CH(CH_3)CO - O]_n -$$

Polylactic acid (PLA) or polylactide

Polymers with a molecular weight between 180 000 and 260 000 are used in the production of melt-spun fibres (Eling et al. 1982), while a molecular weight between 350 000 and 530 000 is needed for the production of solution-spun fibres (Gogolewski and Pennings 1983).

2.2.3. Biodegradation

PLA is mainly degraded by a non-specific hydrolysis to monomers in an aqueous environment (Miller et al. 1977, Williams 1979, Gilding 1981), and, to a lesser extent, through non-specific enzymatic action (Williams 1981, Hollinger and Battistone 1986).

Figure 2 shows the route of metabolism of polylactic acid in vivo (Kulkarni et al. 1966, Lehninger 1982, Hollinger and Battistone 1986). Polylactic undergoes hydrolytic de-esterification into lactic acid which is transformed to pyruvate by lactate dehydrogenase. Pyruvate is decarboxylated into acetyl co-enzyme A which is incorporated into the tricarboxylic acid cycle to form energy, carbon dioxide, and water. The degradation products of PLA are extreted mainly through lungs in ex-

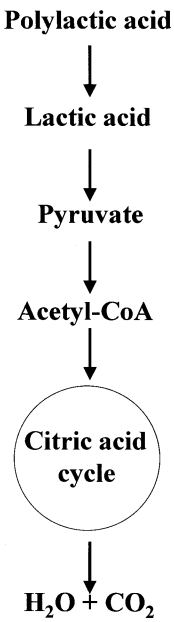


Figure 2. Biodegradation of polylactide (Kulkarni et al. 1966, Lehninger 1982, Hollinger and Battistone 1986).

haled carbon dioxide (up to 97 %), but also via the urine and faeces (Brin 1965, Tubbs 1965, Kulkarni et al. 1966, Brady et al. 1973, Miller et al. 1977, Brandt et al. 1984, Giesecke and von Wallenberg 1985).

Williams (1981) found that certain enzymes, such as pronase, proteinase-K, and bromelain, increased the hydrolysis rate of PLA *in vitro*, while lactate dehydrogenase showed an entirely opposite effect. The rate of degradation also varies greatly with different physical and chemical characteristics, such as molecular weight and the enantiomeric composition of the polymer, the size and shape of the implant, and with environmental factors, methods of processing, and sterilization. A wide range of resorption rates have been reported for these substances (Cutright et al. 1971, Kulkarni et al. 1971, Getter et al. 1972, Brady et al. 1973, Miller et al. 1977). The reported discrepancies were appreciated by Reed and Gilding (1981) and Vert et al. (1981) who investigated and distinguished the effect of different molecular composition parameters on the degradation rate and found that poly-L-lactide degrades most slowly.

The final degradation time of PLLA is still unclear, but reports of more than 5.7 years of degradation times have been published with zygomatic bone fractures treated using high-molecular poly-L-lactic acid (PLLA) bone plates and screws placed on the bone (Bergsma et al. 1995). The copolymer of D- and L-lactide seems to have a shorter degradation time than poly-L-lactide (Vert et al. 1986, Pohjonen et al. 1989, Majola 1992, Suuronen et al. 1992).

2.2.4. Biocompatibility

2.2.4.1. Experimental studies

In the literature the biocompatibility of PLA within bone has been reported to be favourable in the maxillofacial area (Cutright et al. 1971, Kulkarni et al. 1971, Cutright and Hunsuck 1972, Getter et al. 1972, Cutright et al. 1974, Leenslag et al. 1987, Bos et al. 1989a, 1989b, Rozema et al. 1989, Suuronen 1991) and in the cancellous bone area (Vert et al. 1984, Eitenmüller et al. 1987, Räihä et al. 1990, Majola et al. 1991, Matsusue et al. 1991, Manninen et al. 1992a, Päivärinta et al. 1993), and PLA also seems to have some osteogenic potential (Hollinger 1983, Schmitz and Hollinger 1988).

In one study the SR-PLLA plugs were used in the fixation of transverse distal femoral osteotomies in rabbits and followed up to 24 weeks (Pihlajamäki et al. 1994d). The biocompatibility of the implant was found excellent. In another study with the same cancellous bone osteotomies of the distal rabbit femurs, the number of inflammatory cells at the tissue-implant interface was low (Pihlajamäki et al. 1994b).

Intraosseally placed SR-PLLA plates in the fixation of distal femoral osteotomies in rabbits demonstrated that they were suitable for fixation of weight-bearing cancellous bone osteotomies (Koskikare et al. 1996), as were also SR-PLLA plates implanted on both sides of bone (Koskikare et al. 1997a). When comparing intra- and extraosseally implanted SR-PLLA plates to each other in the fixation of distal femoral osteotomies in the same animals, the intraosseally implanted plates did not seem to diminish the amount of trabecular bone (Koskikare et al. 1997b). Intraosseally implanted SR-PLLA screws and pins have been shown to cause similar, mild host tissue responses as seen with corresponding metallic devices, without signs of inflammatory reactions during a follow-up of 48 weeks (Viljanen et al. 1997a, 1997b).

Fifty PLLA plates (20 x 10 x 1 mm) and 50 control plates of medical-grade polyethylene of the same shape were implanted subcutaneously into rats, and mesenchymal tumours arose in 22 out of 50 PLLA implanted rats and in 23 out of 50 control rats (Nakamura et al. 1994). Oppenheimer et al. (1955) showed that long-term implantation of any polymer brings the problem of foreign-body tumorigenesis in rodents (Oppenheimer et al. 1955). On the other hand, in one study, long-

term implantation of poly-L-lactide has been shown to inhibit carcinoma cell growth *in vitro* (Campbell et al. 1994).

Matsusue et al. (1995) implanted ultra-high-strength PLLA rods in the femoral cavity of rabbits. At 18 months histiocytes were observed; from 24 to 36 months their phagocytic activity was maximal, and at 62 months the material had been almost completely absorbed, as there was only a slight residual tissue reaction. Suuronen et al. (1998) fixed mandibular osteotomies in sheep with SR-PLLA multilayer plates (four 0.5-mm-thick plates). After five years in vivo, the material was almost completely resorbed, but small particles of polymer could still be detected at the implantation site. The foreign-body reaction was mainly mild. In an animal study one late foreign-body reaction to polylactide has been reported (Bos et al. 1991). This was around a subcutaneous PLLA plate in a rat 143 weeks after implantation.

Peltoniemi et al. (1998a) studied in sheep the consolidation process of craniotomy lines which were plated with an SR-PLLA plate and narrow titanium miniscrews. During the follow-up time of two years the SR-PLLA had degraded. In another study in sheep using SR-PLLA plates and miniscrews in the calvarium, there were no signs of adverse tissue reaction during 52 weeks (Peltoniemi et al. 1998b). Also in a study of lambs with SR-PLLA miniscrews no clinical foreign-body reaction had occurred during the follow-up time of two years (Peltoniemi et al. 1999a). The biocompatibility and suitability of SR-PLLA plates and miniscrews in the frontal bone craniotomies of growing lambs have been shown (Peltoniemi et al. 1999b). It seems that combinations of PLLA/PDLLA i.ex. poly-96L/4D-lactide (SR-PLLA 96) (Saikku-Bäckström et al. 1999) rods yield promising results in the field of cortical bone osteotomies. Recently it has been also shown that combining transforming growth factor-ß1 to a bioabsorbable SR-PLLA pin (Tielinen et al. 1999) enhances bone formation in the cancellous bone, thus widening the utilizations of bioabsorbable implants.

2.2.4.2. Clinical studies

Clinical manifestations have been reported in zygomatic fractures fixed with PLLA plates after 3.3 to 5.7 years postoperatively (Bergsma et al. 1993, 1995). In 27 small fragment fractures and osteotomies, most commonly chevron osteotomy of the first metatarsal bone for hallux valgus and displaced fracture of the radial head, followed up to 8 - 37 months, no reactions were observed, and biopsy in two patients 20 and 37 months after implantation showed no remaining polymeric material, but the implants were small cylindrical rods of 1.5 or 2.0 mm in diameter (Pihlajamäki et al. 1992).

The use of PLA screws in ankle fractures has been described (Tunc 1991, Bucholz et al. 1994). In one randomized prospective study subtalar extra-articular arthrodesis in children (Partio et al. 1992d) and in the other prospective study talocrural arthodesis in adults (Partio et al. 1992c) were fixed with SR-PLLA pins and screws which appeared to be firm enough to be used for these fixations. In a prospective study, 33 patients were treated with SR-PLLA expansion plugs to fix the transferred coracoid bone block. No re-dislocations occurred, and there was no potential risk of the loosening, breaking or migration, which are common with metal implants (Pihlajamäki et al. 1994e). The SR-PLLA expansion plug was also used for fixation of fractures of the medial malleolus in 26 patients, and the consolidation of the fractures was uneventful with no redisplacements (Pihlajamäki et al. 1994a).

Eitenmüller et al. (1996) used injection-moulded, non-reinforced 3-mm-thick high-molecular-weight PLLA plates for fixation of ankle fractures. Fifty-two per cent of the patients demonstrated an aseptic soft tissue problem caused by delayed clearance of the degrading polylactide particles. In a second study, volume-reduced plates and screws did not cause any soft tissue reactions. Foreign-body reactions caused by high-molecular-weight, as-polymerized PLLA material used

by Bergsma et al. (1993) are not likely associated with all PLLA materials. PLLA materials may differ considerably in the purity of the raw material and in the method of processing.

SR-PLLA meniscus-tacks have been used in the treatment of meniscus lesions (Albrecht-Olsen et al. 1993), ultra-high-strength poly (L-lactide) pins in the fixation of osteochondral fragments of the knee (Matsusue et al. 1996), and SR-PLLA wires combined with SR-PLLA plugs or SR-PGA screws in the fixation of patellar fractures (Juutilainen et al. 1995) with encouraging results. In a preliminary study of 24 patients with rupture of the anterior cruciate ligament (ACL), the patients were operated on using a patellar tendon bone graft fixed with screws and expansion bolts made of SR-PLLA. There were no statistical differences in the results between the SR-PLLA screw and the SR-PLLA expansion bolt (Tuompo et al. 1999b). When SR-PLLA rods were used for fixation of proximal tibial cancellous bone osteotomies and fractures and avulsion fractures, the results were good or moderate (Tuompo et al. 1999a).

2.2.5. Mechanical properties

The mechanical properties of early implants of PLA were poor due to the melt-moulding technique. Poly-L-lactide showed only modest mechanical strength values when manufactured with non-reinforcing techniques (Vainionpää et al. 1989, Matsusue et al. 1991, Majola et al. 1992a). A new manufacturing method, called self-reinforcing, by which implants of sufficient strength could be constructed was introduced (Törmälä et al. 1987, 1988, 1990). The result of the self-reinforced structure, i.e. the fibres are of the same substance as the matrix, was a substantial increase in the strength values for PLA implants. As the initial mechanical strength of PLLA is slightly weaker than that of PGA, an initial bending strength up to 400 MPa has been reported by using this method (Törmälä 1992). Self-reinforced implants can be manufactured with different combinations of the enantiomeric forms DL/LL, resulting in different rates for strength (Majola et al. 1992a). It has been found that the strength loss was faster *in vivo* than *in vitro* (Suuronen et al. 1992, Pohjonen et al. 1997).

Manninen et al. (1992b) studied SR-PLLA screws and metallic screws in the fixation of osteotomies in sheep and found that stress-protection and mechanical weakening could be avoided by using SR-PLLA screws instead of metallic screws. In one study with intramedullary nailing of cortical bone osteotomies in rabbits with SR-PLLA rods manufactured by the fibrillation method it was demonstrated that these rods were strong enough for cortical bone fracture fixation (Manninen and Pohjonen 1993).

The consolidation of a transverse transcondylar osteotomy of the distal rabbit femur, fixed with an SR-PLLA expansion plug, was studied mechanically, and the fixation properties were satisfactory in the 24-week follow-up time, as the mean shear strength was 3.5 – 4.3 MPa in these specimens and 3.6 MPa in the control distal femurs (Pihlajamäki et al. 1994c). SR-PLLA implants have been successfully used in weight-loading cancellous bone osteotomies (Majola 1991), in cortical bone osteotomies in experimental studies (Majola et al. 1992b), and in clinical studies of subcapital femoral osteotomies (Jukkala-Partio et al. 2000).

3. AIMS OF THE PRESENT STUDY

The aims of the present study were to find answers to the following questions:

1. Which are the tissue responses in cancellous bone after implantation with self-reinforced polyglycolic acid (SR-PGA) or self-reinforced poly-L-lactic acid (SR-PLLA) pins in the same rat?

2. Which are the tissue responses in osteotomized cancellous bone after fixation with self-reinforced polyglycolic acid (SR-PGA) or self-reinforced poly-L-lactic acid (SR-PLLA) pins in the same rat?

3. What are the shear-load carrying capacities of cancellous bone implanted with self-reinforced polyglycolic acid (SR-PGA) or self-reinforced poly-L-lactic acid (SR-PLLA) pins in the same rat?

4. What are the shear-load carrying capacities of osteotomized cancellous bone after self-reinforced polyglycolic acid (SR-PGA) or self-reinforced poly-L-lactic acid (SR-PLLA) pin fixation in the same rat?

4. MATERIALS AND METHODS

4.1. FIXATION DEVICES

The implants studied were made of self-reinforced polygycolide (Biofix® SR-PGA) and self-reinforced poly-L-lactide (Biofix® SR-PLLA) pins (Bionx Implants Ltd, Tampere, Finland). Polyglycolide sutures (Dexon "S", size USP 2, manufacturer Davis and Geck, Great Britain) were used as raw material of the self-reinforced polyglycolide pins for both the matrix and reinforcing fibres. The sutures were sintered into pins which had an initial three-point bending strength of 300 MPa and a bending modulus of 11 GPa (tested using a Lloyd 6000R materials testing machine at gross-head speed of 5 mm/min.). The initial shear strength of the SR-PGA pins was 210 MPa (tested at gross-head speed of 10 mm/min. by modifying standard BS 2782, method 340B) (Törmälä 1992).

Self-reinforced polylactide pins were manufactured into self-reinforced (SR-) fibres-in-matrix of the same polymer composite texture by the solid state drawing method. The PLLA raw material used for manufacturing the pins was purified medical-grade polymer obtained from Purac Biochem bv (Gorinchem, Holland). The SR-PLLA implants were manufactured by the die drawing method (Törmälä 1992). The viscosity average molecular weight (M_v) of the raw polymer was 660 000. The draw ratio was 9. The SR-PLLA pins had an initial three-point bending strength of 280 MPa and a bending modulus of 9 GPa (tested similarly to SR-PGA pins). The initial shear strength of the pins was 170 MPa (tested similarly to SR-PGA pins).

In *Study I*, where the tissue reactions were studied, 51 cancellous bones of the distal femurs of the same rat were implanted either with SR-PGA (n=51) or SR-PLLA (n=51) pins of 2.0 mm in diameter and of 15 mm in length. In *Study II*, where the tissue reactions were investigated, 49 SR-PGA and 49 SR-PLLA pins (diameter 2.0 mm, length 15 mm) were fixed in the cancellous bone osteotomies of the distal rat femurs. In *Study III*, where the shear-load carrying capacities were studied, 40 SR-PGA pins (diameter 2 .0 mm, length 15 mm) and 40 SR-PLLA pins of the same sizes were implanted in both femurs of 40 rats. In *Study IV*, where the shear-load carrying capacities were investigated, the distal femurs of 40 rats were osteotomized and fixed with an SR-PGA (n=40) and SR-PLLA (n=40) pin of 2.0 mm in diameter and 15 mm in length .

The SR-PGA pins were sterilized by ethylene oxide and the SR-PLLA pins by gamma-radiation at a minimum dose of 2.5 Mrads (Kolmi, Ilomantsi, Finland).

4.2. EXPERIMENTAL ANIMALS AND ANAESTHETIC PROCEDURE

A total of 208 Wistar rats of both sexes with a mean weight of 415 g (range 220-725 g) and a mean age of 13.5 weeks (range 8-25 weeks) were used in the present study (Table 1). In the pilot studies, six rats were operated on. These rats were not included in the study.

First the rats inhalated carbon dioxide to drop off, and after that they were anaesthetized with subcutaneous (s.c.) injections of ketamine (Ketalar®; Parke-Davis, Barcelona, Spain) 25 mg/kg and medetomidine (Domitor®; Orion-Farmos, Turku, Finland) 0.3 mg/kg. All rats were injected with 10 000 IU procaine penicillin s.c. (Procapen®; Orion, Espoo, Finland) for injection prophylaxis. Elev-

Table 1. Scheme of self-reinforced polyglycolide (SR-PGA) and self-reinforced poly-levo-lactide (SR-PLLA) pin implantation or 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									
Implantation of cancellous bone	8	8	7	5	6	5	7	5	51
Fixation of osteotomized cancellous bone	5	6	6	7	8	6	6	5	49
Controls	1	1	1	1	1	1	1	1	8
Strength studies									
Shear-load carrying capacities of cancellous bone	5	5	5	5	5	5	5	5	40
Shear-load carrying capacities of osteotomized cancellous bone	5	5	5	5	5	5	5	5	40
Controls	2	3	2	2	3	2	3	3	20
Number of rats included in the series	26	28	26	27	28	24	27	24	208
Pilot studies									6
Lost in surgery (3) and in anaesthesia (11)									14
Total number of rats									228

en rats died due to an anaesthesia complication and three rats due to surgical complications. They were excluded from the study.

4.3. OPERATIVE TECHNIQUE AND POSTOPERATIVE CARE

Both hind legs of the rats were shaved and scrubbed with antiseptic fluid (Neo-Amisept®; Orion-Farmos, Turku, Finland). A medial longitudinal parapatellar arthrotomy was made, the patella was dislocated laterally in both knees, and the distal portion of the femur was exposed in both knees of the rat.

A. In *Studies I and III*, a longitudinal drill channel , 2.0 mm in diameter and 15 mm in depth, was made centrally through the intercondylar portion towards the intramedullary canal. An SR-PGA pin (2.0 x 15 mm) was tapped into the right femur canal and an SR-PLLA pin of the same size into the left femur.

B. In *Studies II and IV*, transverse transcondylar osteotomies were made with a circular saw in the cancellous bone of the distal femurs.

The osteotomies were reduced exactly, and channels of 2.0 mm diameter and 15 mm length were drilled perpendicular to the osteotomy line from the intercondylar space of the distal femurs toward the intramedullary canal through the metaphysis. The osteotomies were fixed with a 2.0 mm SR-PGA pin in the right femur and with a 2.0 mm SR-PLLA pin in the left femur.

The pins were tapped into the level of the articular surface of the intercondylar notch to allow free mobility of the knee joints. The incisions were closed in layers with 3-0 polyglycolide sutures (Dexon®; Davis and Geck, Gosport, United Kingdom). Radiographs were taken postoperatively. The distance between the roentgen tube (Siemens, Tridoros 5S, Erlangen, Germany) and the target was 90 cm, and the exposure factors were 40 kV, 5.0 mAs, and 0.03 seconds. The rats were returned alone into single cages where they recovered from the anaesthesia before they were allowed to join in pairs in a larger cage. All rats were fed *ad libitum* and allowed to use their limbs freely without external support.

4.4. TISSUE SAMPLING TECHNIQUES

Three days before killing the rats received an intramuscular injection of oxytetracycline (OTC) (Terramycin®; Pfizer, Brussels, Belgium) 50 mg/kg to make newly formed bone visible for tetracycline labelling studies (Milch et al. 1958).

The rats were killed with an overdose injection of sodium pentobarbital (Mebunat®; Orion, Espoo, Finland) 60 mg/kg. Both femurs were exarticulated and dissected free of all soft tissue. Radiographs were taken in anteroposterior and lateral views after dissection. The distal thirds of each femur were fixed in a series of ethanol immersions with increasing concentrations (70-99%) and then embedded in methylmethacrylate (Schenk 1965, Baron et al. 1983). For histologic and histomorphometric analyses 5-µm thick sections were cut with a Polycut S microtome (Reichert-Jung, Nussloch, Germany) in the coronal plane and stained by the Masson-Goldner trichrome method (Goldner 1938). For microradiographic and tetracycline labelling studies, 80-µm thick longitudinal sections were cut with a Leitz 1600 saw microtome (Ernst Leitz Wetzlar, Wetzlar, Germany). The microradiographs were made using the Faxitron X-ray system, Model 43855 A (Hewlett-Packard, McMinnville, OR) and high resolution plates, ultraflat, Type 1A (Imtec Products, Sunnyvale, CA). The histologic, oxytetracycline fluorescence, and microradiographic specimens were studied with a Diaplan microscope (Ernst Leitz Wetzlar), and the fluorescence microscopy was performed using an HBO 220 ultraviolet lamp (Osram, Berlin, Germany) and a BG 812/6 primary filter (Ernst Leitz Wetzlar). Polarizing microscopy was used to identify birefringent polymeric material in the specimens.

For the quantitative histomorphometric evaluation a Leitz microscope was linked via a television videocamera to a semiautomatic computerized image analyzer Videoplan, (Kontron, Munich, Germany), and magnifications of x100 and x400 were used. Eight follow-up groups (from one to 52 weeks) of five rats operated with or without osteotomy and one control rat were investigated. Thus, there were 176 longitudinal histologic sections from 80 surgically treated rats and eight control rats. From each section, two fields on the lateral and two on the medial side of the pin (704 fields including control rats) were delineated in the surgically treated rats at the tissue-implant interface using the point 1.5 mm from the orifice of the implant channel as a reference so that there were two fields on the lateral and two fields on the medial sides of the pin without osteotomy (Fig. 3) or with osteotomy (Fig. 4). The site of the original tissue and implant boundary was determined with the aid of a scale plate placed over the microscopic field (Revell 1983). To avoid any

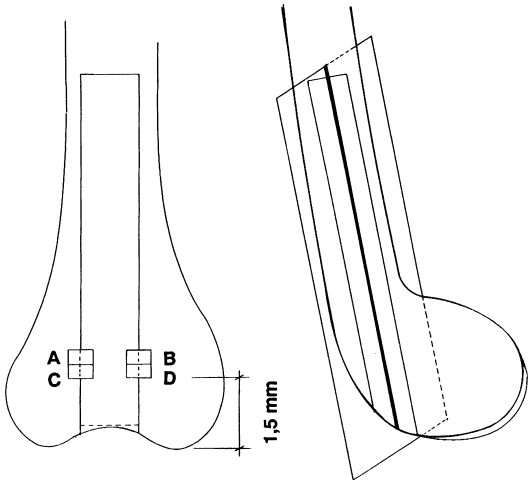


Figure 3. Schematic anterior and lateral views of the distal rat femur showing the positioning of the pin and the four standardized sample fields (A, B, C, D) each measuring 0.31 x 0.61 mm.

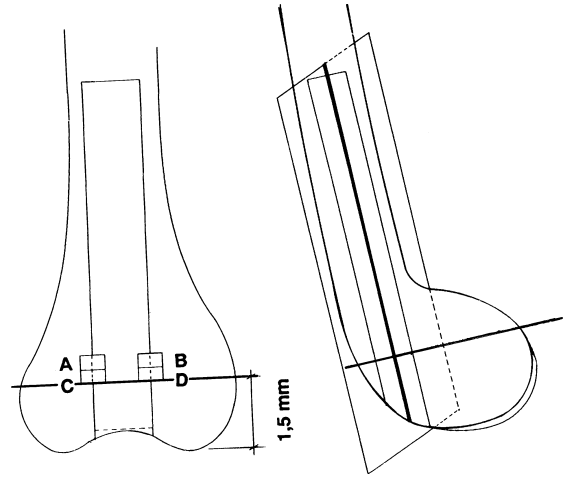


Figure 4. Schematic anterior and lateral views of the rat distal femur showing the positioning of the pin, the site of osteotomy, and the site of the standardized sample fields (A, B, C, D) each measuring 0.31 x 0.61 mm.

bias caused by interobserver variation, one investigator performed all visual assesments. Solid union was considered to have occurred if the number of trabeculae bridging the osteotomy amounted to more than 2/3 of the average of the intact control specimens.

Within the 0.31 x 0.61 mm sample fields, the interface was examined at a magnification of x100 for histomorphometry and of x400 for cell identification. The histomorphometric variables analysed were the total trabecular bone area (including calcified trabeculae and osteoid), the total osteoid surface fraction, and the active osteoid formation surface over the entire trabecular surface and the area occupied by the implant within the sample field (Frost 1983). The ongoing calcification of the osteoid was confirmed by fluorescence microscopy and microradiography (Jowsey et al. 1965). Direct influence of the osteotomy was avoided by making the histomorphometric measurements proximal to the osteotomy level. The concentrations of phagocytic macrophages and foreign-body giant cells were counted per medium power field (x400). The results are given as pooled mean values.

4.5. TESTING THE SHEAR-LOAD CARRYING CAPACITIES OF CANCELLOUS BONE FIXED WITH SELF-REINFORCED POLYGLYCOLIC ACID (SR-PGA) OR SELF-REINFORCED POLY-L-LACTIC ACID (SR-PLLA) PINS

The shear-load carrying capacities of 80 pairs of femurs with or without osteotomy were investigated. The bone specimens were retained at 22-23°C in 0.9 % saline solution before mechanical testing which was performed within 24 h., after the death of the rat. The proximal ends of the operated bone specimens were embedded in Acryfix SQ®, (Struers, Rødovre/Copenhagen, Denmark) cold mounting acrylic resin. The shear-load carrying capacities, i.e. force at fracture during the test = F (N), were measured at room temperature (r.t.; from 22-23°C) using a JJ 5003 tensile testing equipment (J.J. Lloyd Instruments, Southampton, UK) with a testing speed of 10 mm/min. (Fig. 5). The 20 pairs of control intact femurs were tested in the same way.

4.6. STATISTICAL ANALYSIS

For statistical analyses the paired t-test was used (I-IV). The two-way analysis of variance (ANOVA) was used to study differences attributable to time and Tukey´s HSD (honestly significant differences) test for determining the individual differences in time direction (Sokall and Rohlf 1995). The “meta-analysis” was done to compare both histologic and strength studies without osteotomy to studies with osteotomy using the same statistical tests.

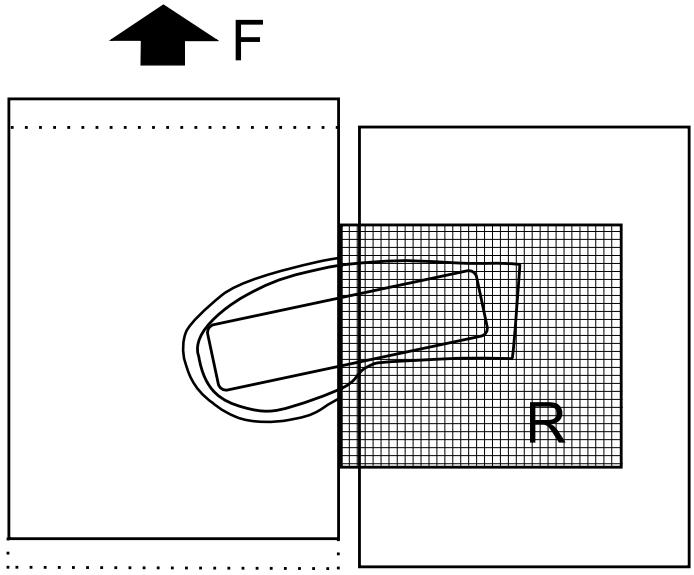


Figure 5. Measuring of the shear-load carrying capacity of the femurs. F = shear force at fracture. R = Acryfix SQ®, cold mounting acrylic resin, in which a bone was embedded before testing. The testing speed was 10 mm/min. The cortical bone was not removed. The testing tool fixed the specimens so that only the shear-load component was applied.

5. RESULTS

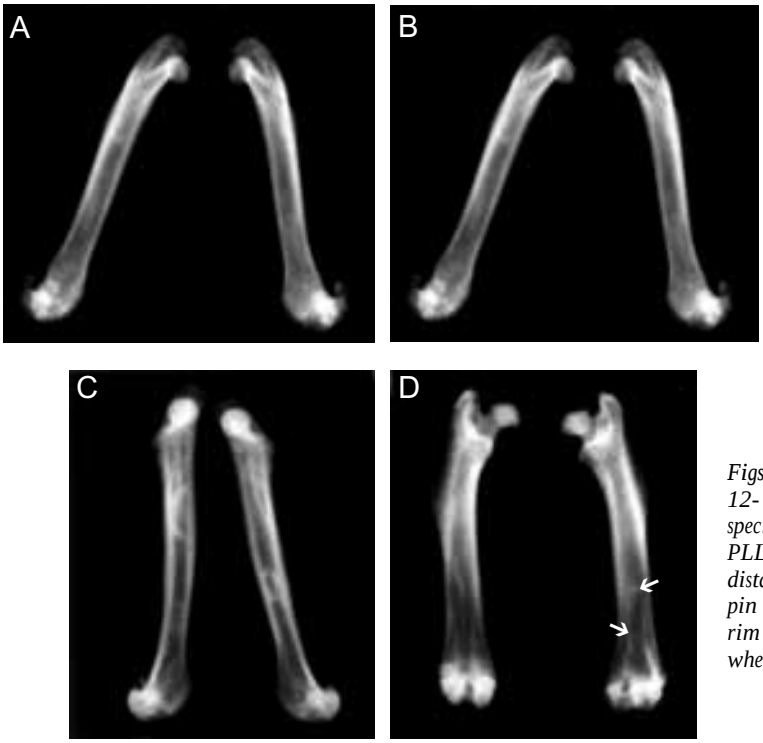
5.1. HISTOLOGIC STUDIES

5.1.1. Biocompatibility and bioabsorption of self-reinforced polyglycolic acid (SR-PGA) and self-reinforced poly-L-lactic acid (SR-PLLA) pins in the cancellous bone tissue of rat

The biocompatibility of the SR-PGA and SR-PLLA pins was good, as only a mild inflammatory tissue reaction in both implant types was seen. These two polyester implants seemed to result in an osteostimulatory response at the tissue-implant interface after implantation into the cancellous bone of the distal rat femur.

5.1.1.1. Radiography

The implants were radiolucent and it was difficult to detect the drill channels of the pins. However the channels were detectable at 52 weeks after operation showing the degraded implant of SR-PGA, whereas SR-PLLA pin was intact during the whole follow-up time. (Figs. 6 A-D)



Figs. 6 A-D Radiographs of one- (A), 12- (B), 24- (C), and 52-(D) week specimens after SR-PGA-(left) and SR-PLLA-(right) implantation in the rat distal femur. At 52 weeks SR-PLLA pin is still intact and there is an osseous rim surrounding it (white arrows), whereas SR-PGA pin has degraded.

5.1.1.2. Histology, microradiography, and oxytetracycline fluorescence studies

One week. Strong new-bone formation with osteoblast columns in the trabecular network in the metaphyseal area around both the SR-PGA (Fig. 7 A) and the SR-PLLA (Fig. 7 B) pin was detected. In direct contact to the pins there were some macrophages, giant cells, and fibroblasts surrounded by osteoblast columns. This was confirmed by microradiography and oxytetracycline fluorescence (OTC) studies in which new bone was seen around the pins.

Three weeks. Active bone marrow was seen near the pin with a thin layer of fibrous tissue. A few giant cells and macrophages were surrounded by a thin new-bone line around the SR-PGA (Fig. 8 A) and SR-PLLA (Fig. 8 B) pins. New-bone formation around the pins was also detected in the microradiographic and oxytetracycline studies. The beginning of the degradation of the SR-PGA implant could be seen, though the implant-tissue border was still distinct. The gross geometry of the SR-PLLA pin was intact.

Six weeks. The new-bone layer was thicker and the fibrous layer with some macrophages and giant cells thinner around the SR-PGA (Fig. 9 A) and SR-PLLA (Fig. 9 B) pins. The granulation tissue invasion into the SR-PGA pin was more evident than at three weeks. The SR-PLLA pin was intact.

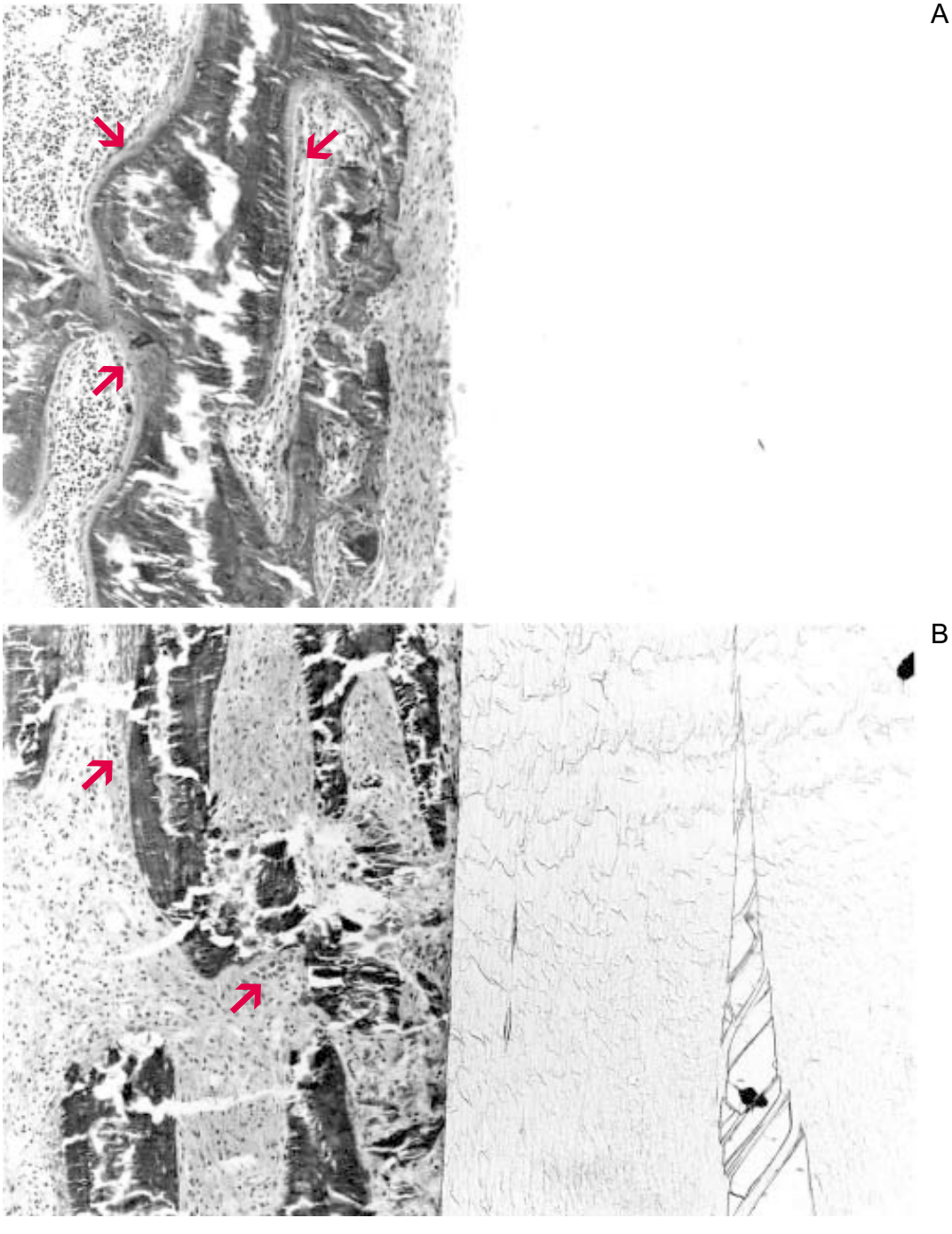
12 weeks. Granulation tissue penetrated into the fibres of the SR-PGA pin, which was surrounded by foam-like macrophages (Fig. 10 A). There was a thin connective tissue layer with a few phagocytic giant cells between a thick bone tube and the SR-PLLA pin (Fig. 10 B). New-bone formation was seen especially in the tissue-implant border in the SR-PGA-implanted specimen, which was confirmed by microradiographic and oxytetracycline studies. The SR-PLLA pin was still intact.

24 weeks. The SR-PGA implant was almost completely degraded. Connective tissue had replaced the site of the pin and it was surrounded by osteoblasts and osteoid. There was a thick bone layer on both sides of the pin (Fig. 11 A). Around the SR-PLLA implant there was thin connective tissue with a few giant cells, and the osseous rim was thicker than before. The geometry of the SR-PLLA implant was still intact (Fig. 11 B). The microradiographic and oxytetracycline studies showed only a weak new-bone formation in both fixed bones.

36 weeks. There was no birefringent SR-PGA material left, and the implant channel was replaced mostly by bone marrow cells and connective tissue. On both sides there were bone layers. In the distal part of the SR-PLLA pin there was more connective tissue with a few phagocytic cells than in the proximal part. The bone tube had become slightly thicker. Nearly no signs of new-bone formation could be seen. The tissue-implant border of SR-PLLA was distinct.

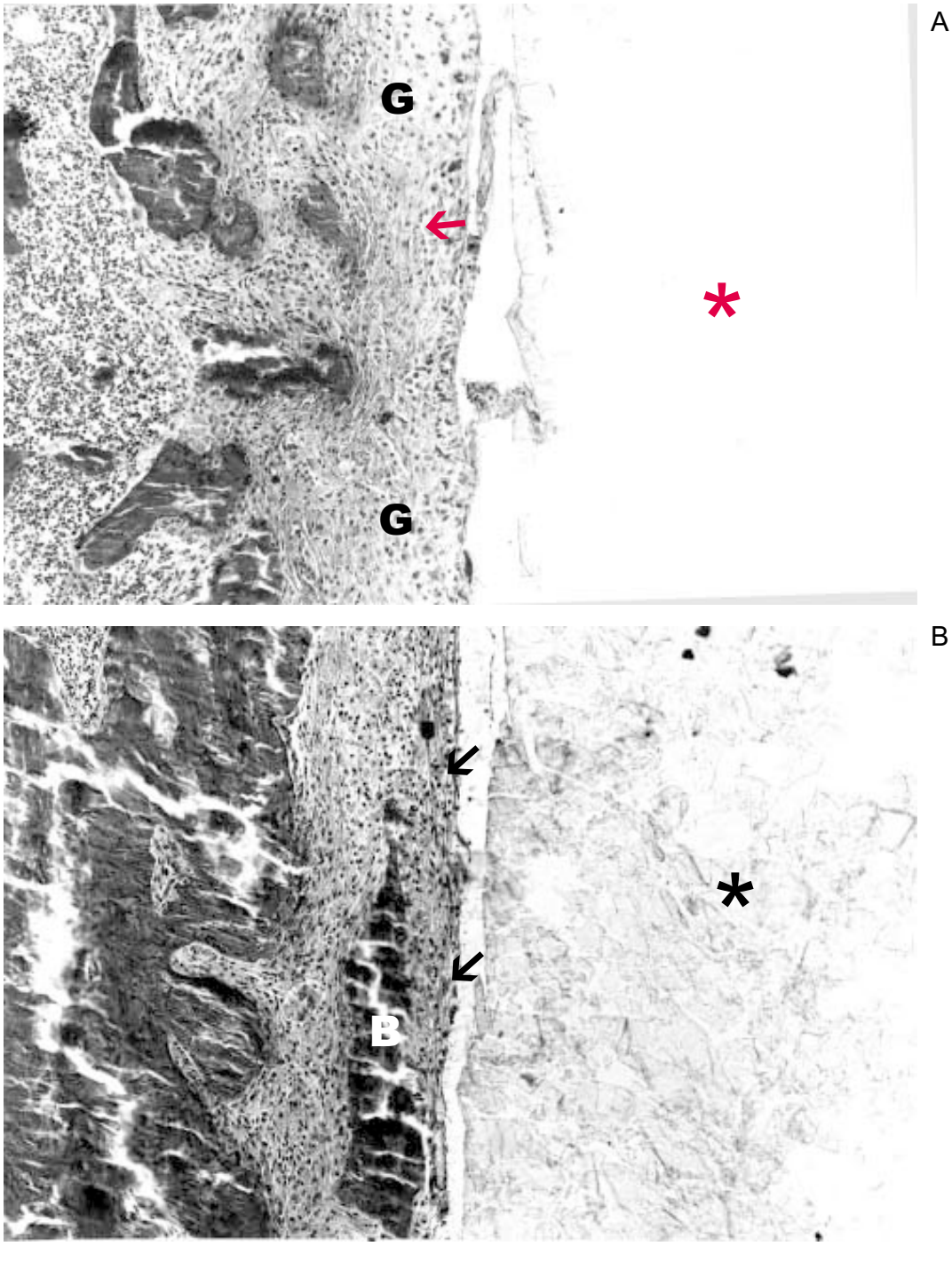
48 and 52 weeks. The SR-PGA pin had totally degraded, and the bone remodelling was still going on (Fig. 12 A). The connective tissue with some phagocytic cells and the bone layer were surrounding the SR-PLLA pin as at 36 weeks. There were no visually seen changes in the bioabsorption of the SR-PLLA pin, as the tissue-implant border was still distinct. (Fig. 12 B). This was confirmed by microradiography and oxytetracycline fluorescence (OTC) studies in which new bone was seen as a trabecular bone network (Figs. 13 A-B).

Photomicrographs of the tissue-implant boundary of a distal rat femur at a follow-up 1, 3, 6, 12, 24, and 52 weeks after SR-PGA and SR-PLLA pin implantation (Figs. 7-12).



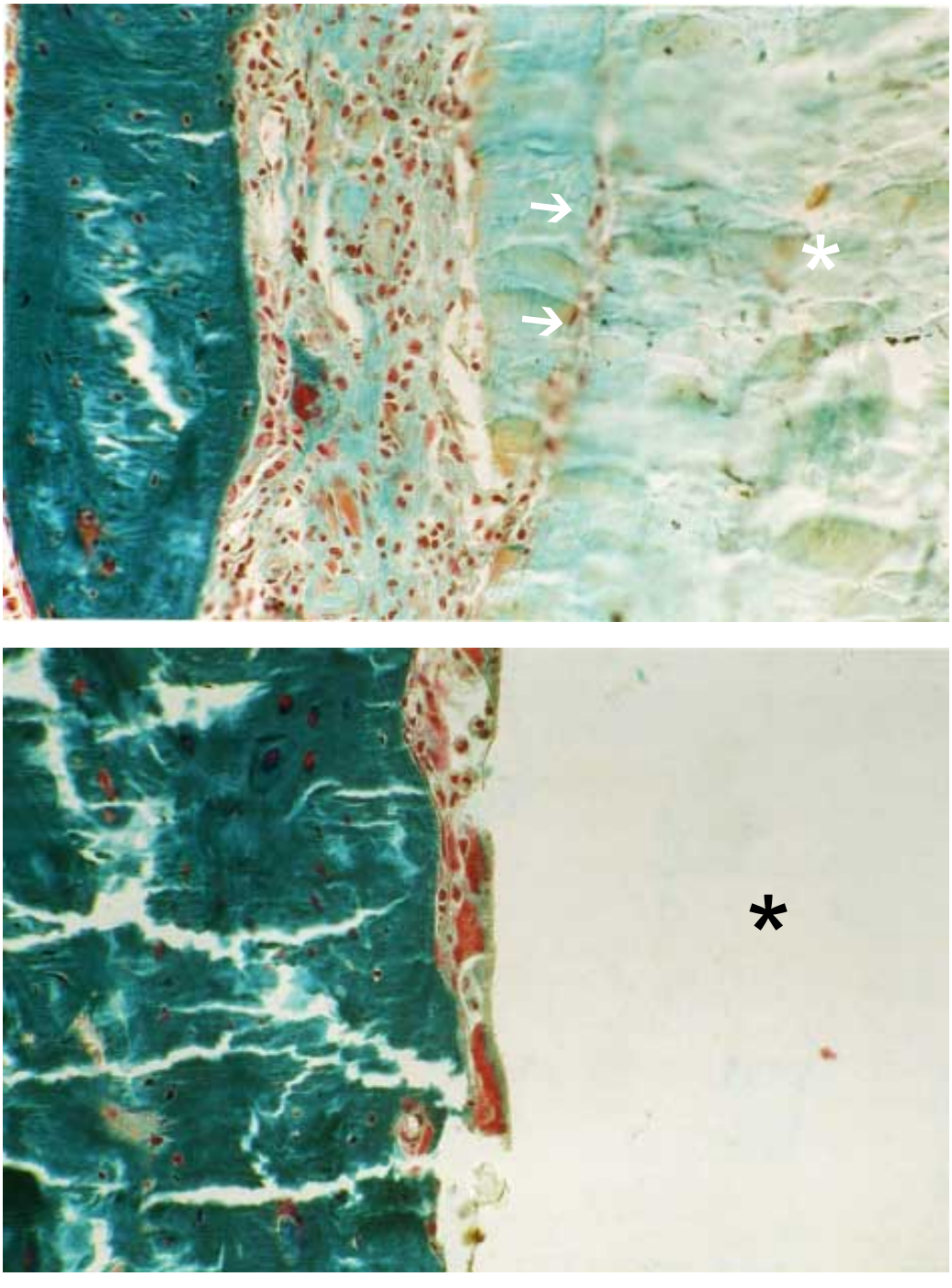
Figs. 7 A-B. At one week a vigorous osteostimulatory response i.e. osteoblasts (red arrows) is seen in the metaphyseal area after SR-PGA pin (A) and SR-PLLA pin (B) implantation. (Stain, Masson-Goldner; original magnification, x 100).

Photomicrographs of the tissue-implant boundary of a distal rat femur at a follow-up 1, 3, 6, 12, 24, and 52 weeks after SR-PGA and SR-PLLA pin implantation (Figs. 7-12).



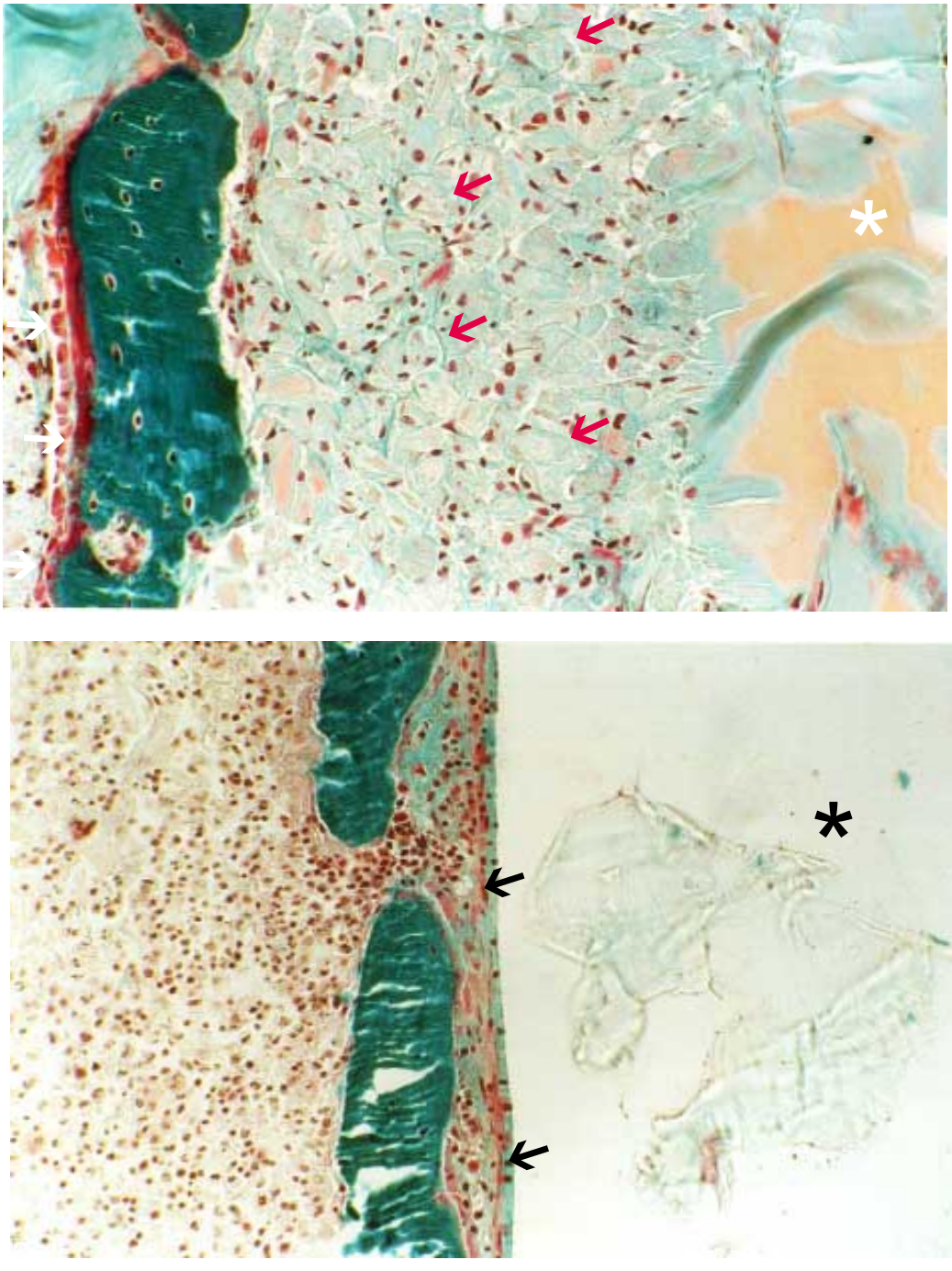
Figs. 8 A-B. At three weeks active granulation tissue (G) and a thin layer of fibrous tissue (red arrow) are seen after SR-PGA pin (red asterisk) implantation (A). A few giant cells (black arrows) are surrounding the SR-PLLA pin (black asterisk) with a thin new-bone line (white B) (B). (Stain, Masson-Goldner; original magnification, x 100).

Photomicrographs of the tissue-implant boundary of a distal rat femur at a follow-up 1, 3, 6, 12, 24, and 52 weeks after SR-PGA and SR-PLLA pin implantation (Figs. 7-12).



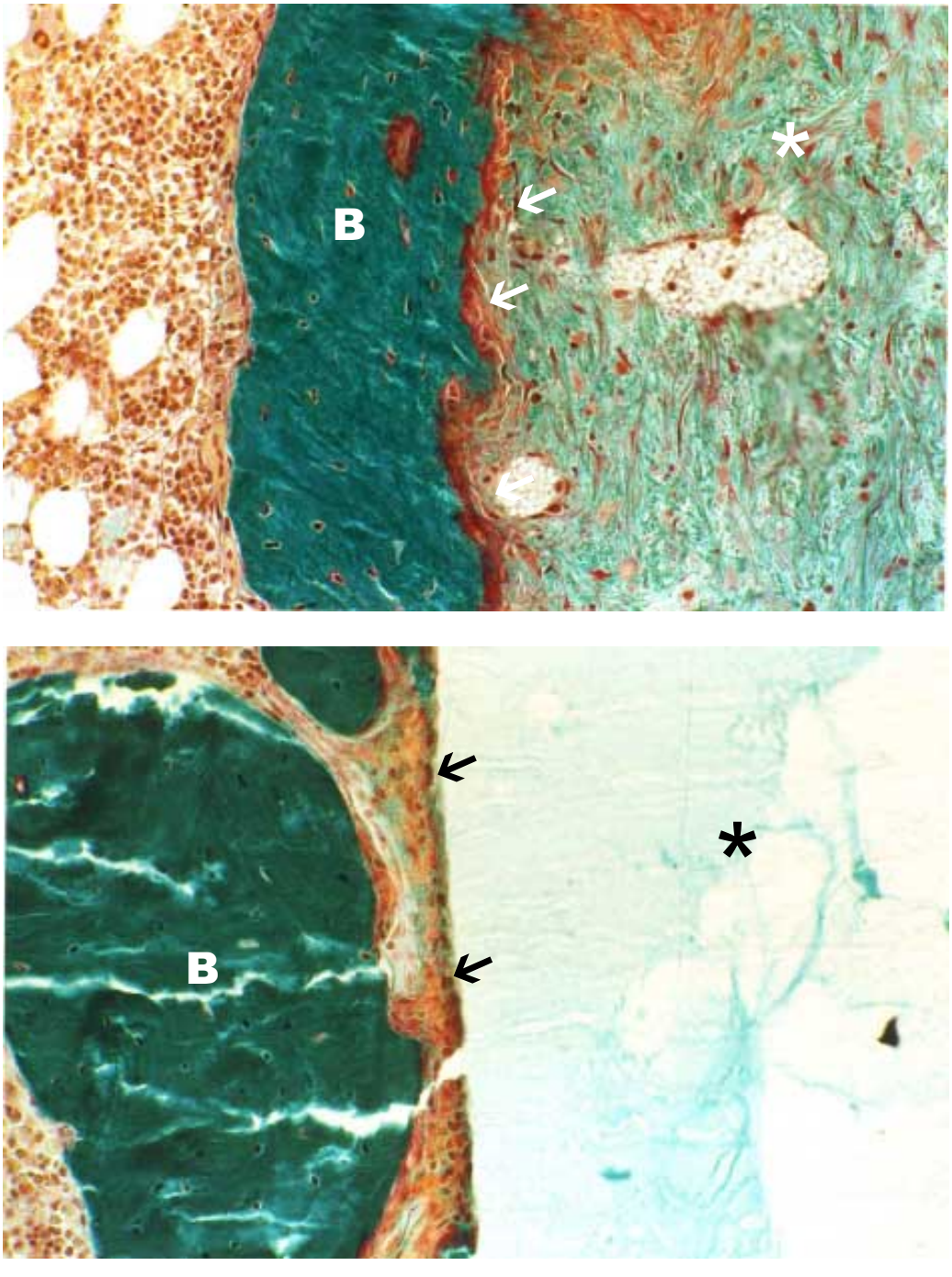
Figs. 9 A-B. In a 6-week specimens the granulation tissue (white arrows) is invaded into the SR-PGA pin (white asterisk) (A). No signs of host tissue penetrations into the SR-PLLA pin (black asterisk) can be seen (B). (Stain, Masson-Goldner; original magnification, x 100).

Photomicrographs of the tissue-implant boundary of a distal rat femur at a follow-up 1, 3, 6, 12, 24, and 52 weeks after SR-PGA and SR-PLLA pin implantation (Figs. 7-12).



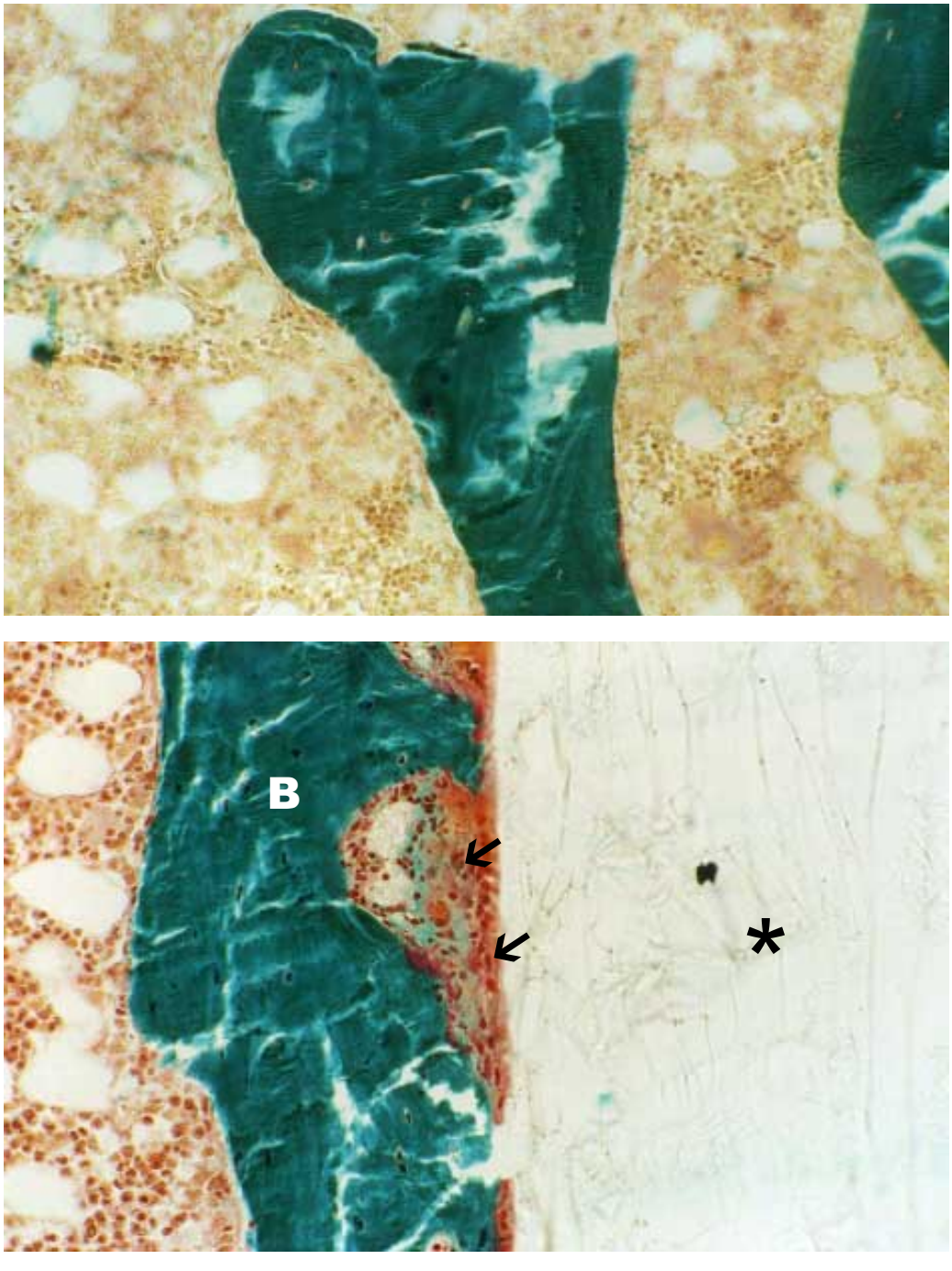
Figs. 10 A-B. In 12-week specimens a number of foam-like macrophages (red arrows) surround the SR-PGA pin (white asterisk). Several osteoblasts (white arrows) can be seen in the trabecular bone (A). There is a thin connective tissue layer with a few phagocytizing giant cells (black arrows) around the intact SR-PLLA pin (black asterisk) (B). (Stain, Masson-Goldner; original magnification, x 100).

Photomicrographs of the tissue-implant boundary of a distal rat femur at a follow-up 1, 3, 6, 12, 24, and 52 weeks after SR-PGA and SR-PLLA pin implantation (Figs. 7-12).

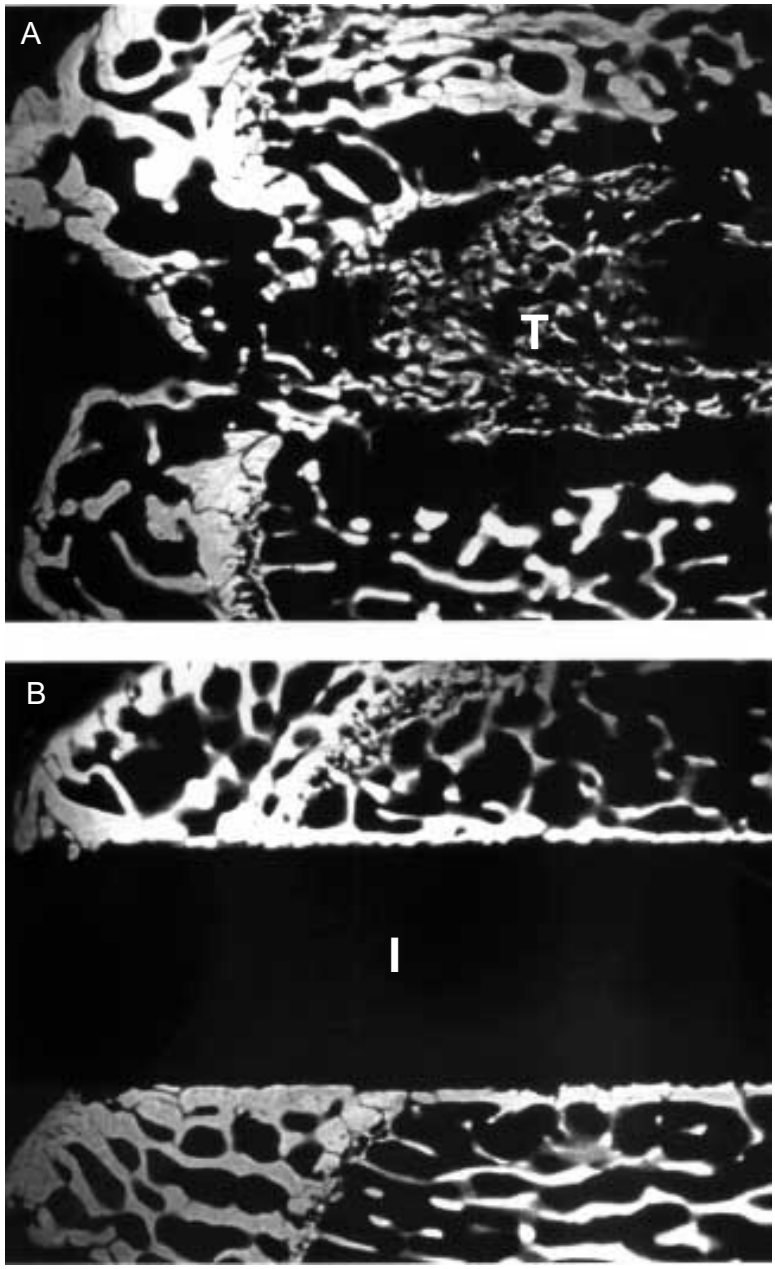


Figs. 11 A-B. At 24-weeks the site of the SR-PGA pin (white asterisk) is replaced by connective tissue and surrounded by osteoblasts (white arrows) and a thick bone layer (white B) (A). A thin connective tissue layer with a few giant cells (black arrows) and a thick osseous rim (white B) are surrounding the SR-PLLA pin (black asterisk) (B). (Stain, Masson-Goldner; original magnification, x 100).

Photomicrographs of the tissue-implant boundary of a distal rat femur at a follow-up 1, 3, 6, 12, 24, and 52 weeks after SR-PGA and SR-PLLA pin implantation (Figs. 7-12).



Figs. 12 A-B. Total bioabsorption of SR-PGA pins had occurred between the follow-up periods of 24 and 36 weeks, and at 52 weeks (A) the bone remodelling is still going on.There are no visually seen changes in the bioabsorption of the SR-PLLA pin in the whole follow-up period, and at 52 weeks (B) a thin connective tissue with a few giant cells (black arrows) surrounds the pin (black asterisk) with a thick osseous rim (white B) (B). (Stain, Masson-Goldner; original magnification, x 100).



Figs. 13 A-B Micrographs of 80 µm-sections as seen at 48 weeks when SR-PGA pin (A) or SR-PLLA pin (B) is implanted in the distal rat femur. SR-PGA pin has degraded and bone remodelling is going on as seen as a trabecular bone network (T). Radiolucent SR-PLLA implant (I) is seen intanct.

5.1.1.3. Histomorphometry

The fractional osteoid surface in the SR-PGA-implanted specimens reached its highest value at 12 weeks after implantation. The SR-PLLA group showed the highest fractional osteoid surface value after one week of implantation. The osteoid surface fraction in the SR-PGA-implanted specimens was more abundant at six, 12, and 24 weeks post-implantation than in the SR-PLLA-implanted specimens (Fig. 14). The most remarkable host cell activity in the new-bone formation was present at 12 weeks, and, at the same time, the number of macrophages reached its maximum (Fig. 15) and the total trabecular bone volume was at its lowest value in the SR-PGA-implanted specimens (Fig. 16). The most trabecular bone was observed at 24 weeks in the SR-PGA- and SR-PLLA-implanted specimens. The rapid increase of the total trabecular bone volume by 24 weeks in the SR-PGA-implanted specimens (Fig. 16) occurred simultaneously with the notable decrease in the number of macrophages (Fig. 15).

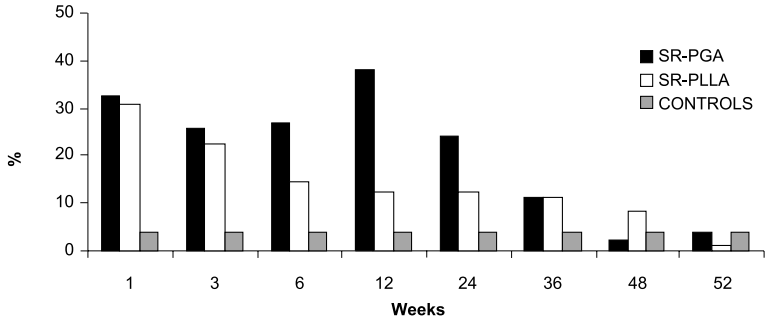
The total bioabsorption of the SR-PGA pins occurred between the follow-up periods of 24 and 36 weeks, and the ultimate clearing of SR-PGA debris was performed principally by macrophages. No signs of degradation of the SR-PLLA pins were observed within the follow-up times (Fig. 17).

Figure 14. The osteoid surface fraction over the total trabecular surface (%) in the distal rat femur 1, 3, 6, 12, 24, 36, 48, and 52 weeks after implantation of an SR-PGA and SR-PLLA pin. The osteoid surface fraction reached its highest values at 12 weeks after SR-PGA implantation and at one week after SR-PLLA implantation. The control value is the mean value of rats killed after each follow-up time.

Figure 15. The number of macrophages (M-F) and giant cells (G-C) at the tissue-implant interface (counted per medium power field, x 400) in the distal rat femur 1, 3, 6, 12, 24, 36, 48, and 52 weeks after implantation of an SR-PGA and SR-PLLA pin. The number of macrophages reached its maximum at 12 weeks after SR-PGA implantation, as the most remarkable host cell activity in the new bone formation was present.

Figure 16. The total trabecular bone area fraction of the total tissue area (%) in the distal rat femur at various time points after implantation of an SR-PGA and SR-PLLA pin. The most trabecular bone was seen at 24 weeks and it was 33.9 % after SR-PGA and 32.6 % after SR-PLLA implantation. It remained over 20 % after that time point. The control value is the mean value of rats killed after each follow-up time.

Figure 17. The area occupied by the implant (%) in the distal rat femur 1 , 3, 6, 12, 24, 36, 48, and 52 weeks after implantation of an SR-PGA and SR-PLLA pin. The total bioabsorption of SR-PGA pins had occurred between 24 and 36 weeks, but no signs of degradation of SR-PLLA pins were observed within the follow-up times.


50
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SR-PGA
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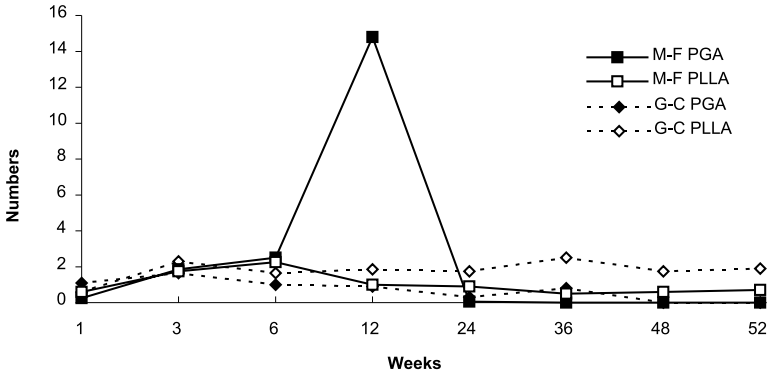
Weeks


16
14
12
10
8
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4
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Numbers
M-F PGA
M-F PLLA
G-C PGA
G-C PLLA
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36
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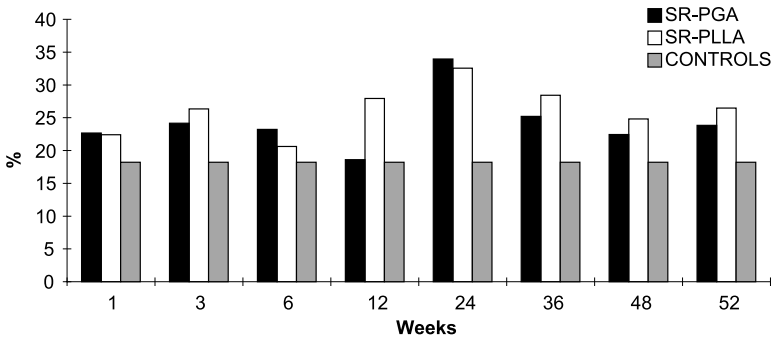
52
Weeks


40
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SR-PGA
SR-PLLA
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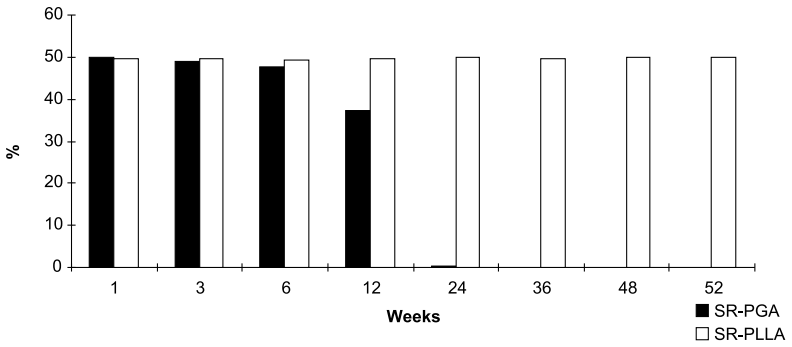
Weeks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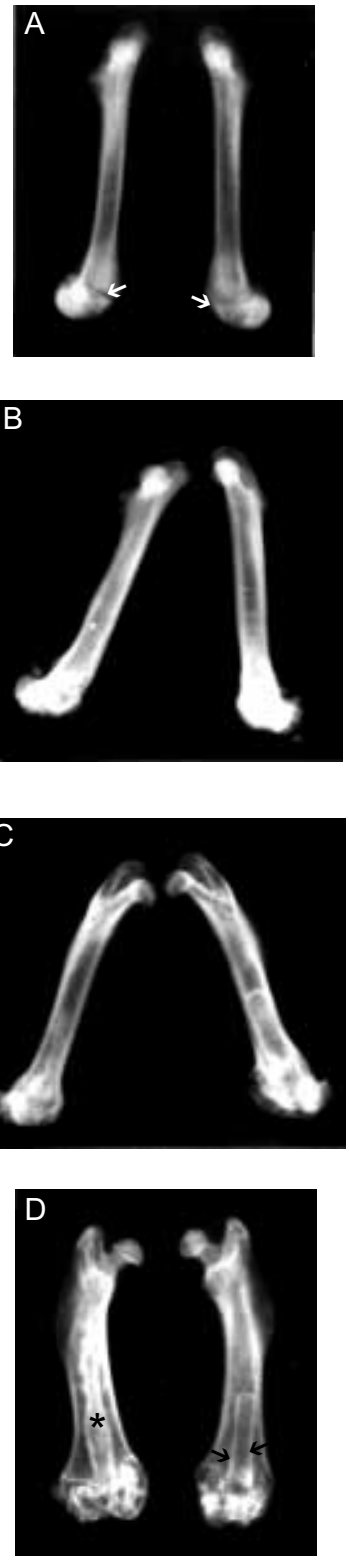
12
24
36
48
52
Weeks
SR-PGA
SR-PLLA

5.1.2. Biocompatibility, bioabsorption, and fixation properties of self-reinforced polyglycolic acid (SR-PGA) and self-reinforced poly-L-lactic acid (SR-PLLA) pins in the osteotomized cancellous bone of rats

The biocompatibility of the SR-PGA and SR-PLLA pins was good. The osteostimulatory effects of these two polyesters were different.

5.1.2.1. Radiography

The osteotomy line was visible in all SR-PGA and SR-PLLA specimens at one week. The radiographs showed a bony union of osteotomies at six weeks in four of the six osteotomies fixed with SR-PGA pins and three of the six fixed with SR-PLLA pins. Six out of seven SR-PGA-fixed osteotomies and five out of seven SR-PLLA-fixed osteotomies were consolidated at 12 weeks.The osteotomies were partly detectable up to 24 weeks as there were three out of eight osteotomies fixed with SR-PGA pins and four out of eight osteotomies fixed with SR-PLLA pins visible. After that the osteotomy lines were not visible except at 48 weeks where in both SR-PGA- and SR-PLLA-fixed bones only one of the six osteotomies was not firmly consolidated (figs. 18 A-D).



Figs. 18 A-D. Radiographs of one- (A), 12- (B), 24- (C), and 52- (D) week specimens after SR-PGA-(left) and SR-PLLA-(right) fixation in the osteotomized rat distal femur. The osteotomy lines (white arrows) are visible at one week specimens. At 52 weeks SR-PGA pin is totally degraded and calcified trabecular bone (black asterisk) can be seen. The SR-PLLA implant-tissue border is still intact and a thick osseous rim (black arrows) is seen.

5.1.2.2. Histology, microradiography, and oxytetracycline fluorescence studies

One week. Intense new-bone formation was seen around the SR-PGA (Fig. 19 A) and SR-PLLA (Fig. 20 A) pins at the osteotomy sites and in the metaphyseal area. A few giant cells and macrophages were in direct contact with both implants and surrounded by osteoblast columns. This was confirmed by microradiography and oxytetracycline fluorescence (OTC) studies.

Three weeks. In both SR-PGA- (Fig. 19 B) and SR-PLLA-fixed (Fig. 20 B) osteotomies two out of six showed solid union. There was strong new-bone formation, which was also seen in the microradiographic and oxytetracycline fluorescence studies. Granulation tissue had started to invade the SR-PGA implant.

Six weeks. The new-bone formation was stronger in both SR-PGA (Fig. 19 C) and SR-PLLA (Fig. 20 C) specimens after pin fixation than at three weeks.There were some phagocytizing macrophages around the SR-PGA pin, into which granulation tissue had invaded . The SR-PLLA pin was microscopically intact.

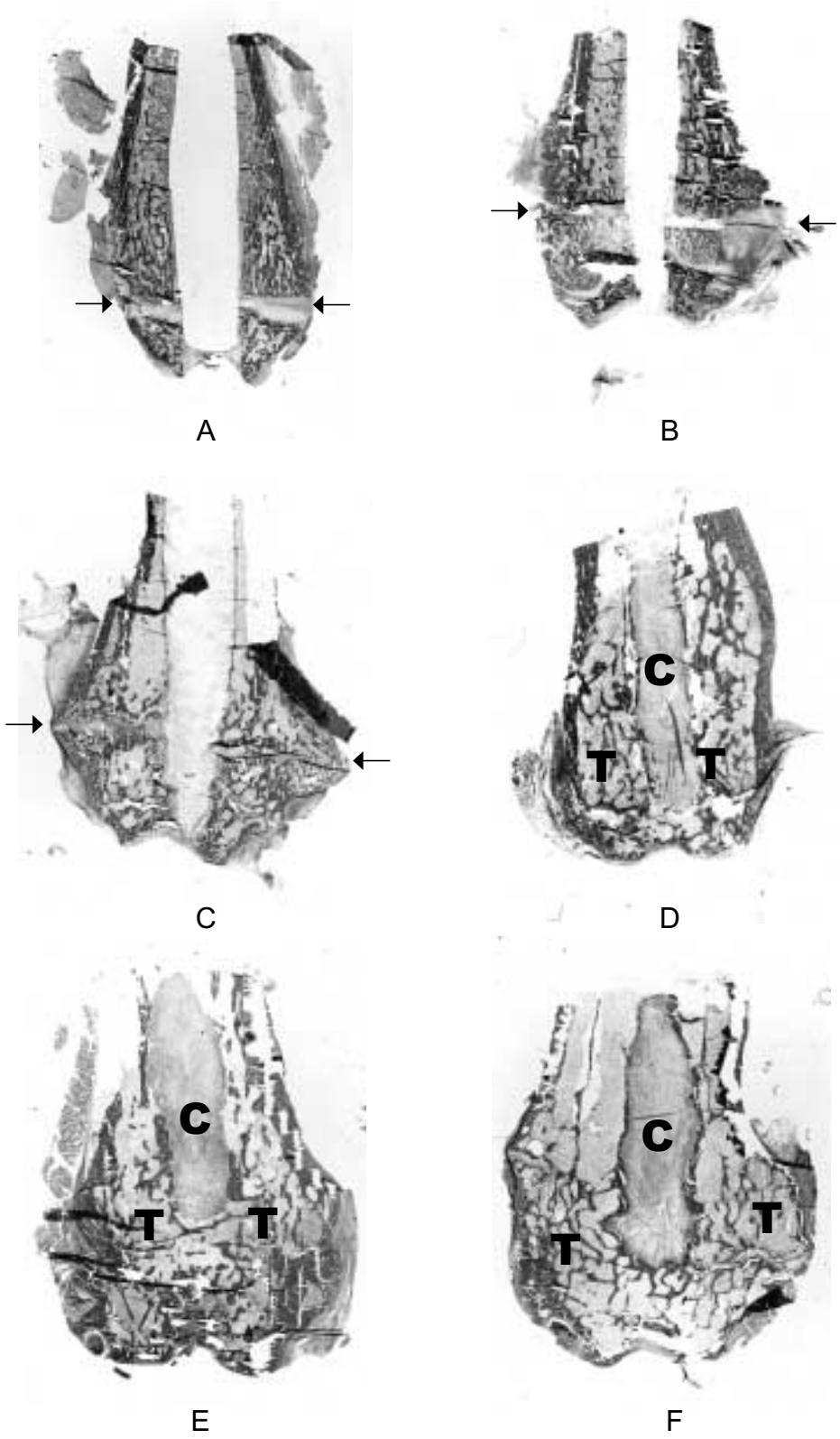
12 weeks. Six out of seven SR-PGA-fixed osteotomies (Fig. 19 D) and five out of seven SR-PLLA-fixed osteotomies (Fig. 20 D) were consolidated. More macrophages were seen in SR-PGA-fixed osteotomies than in those fixed by SR-PLLA. The area occupied by the SR-PGA pin had decreased from the original, whereas the shape of the SR-PLLA pin was intact.

24 weeks. Solid bony union had occurred in five out of eight osteotomies fixed with SR-PGA pins (Fig. 19 E) and in four out of eight osteotomies fixed with SR-PLLA pins (Fig. 20 E). The new-bone formation was more active in the SR-PGA-fixed osteotomies than in the SR-PLLA-fixed osteotomies, which was confirmed by oxytetracycline labelling studies and microradiographically. The SR-PGA pin had almost degraded, as the SR-PLLA implant-tissue border was still intact.

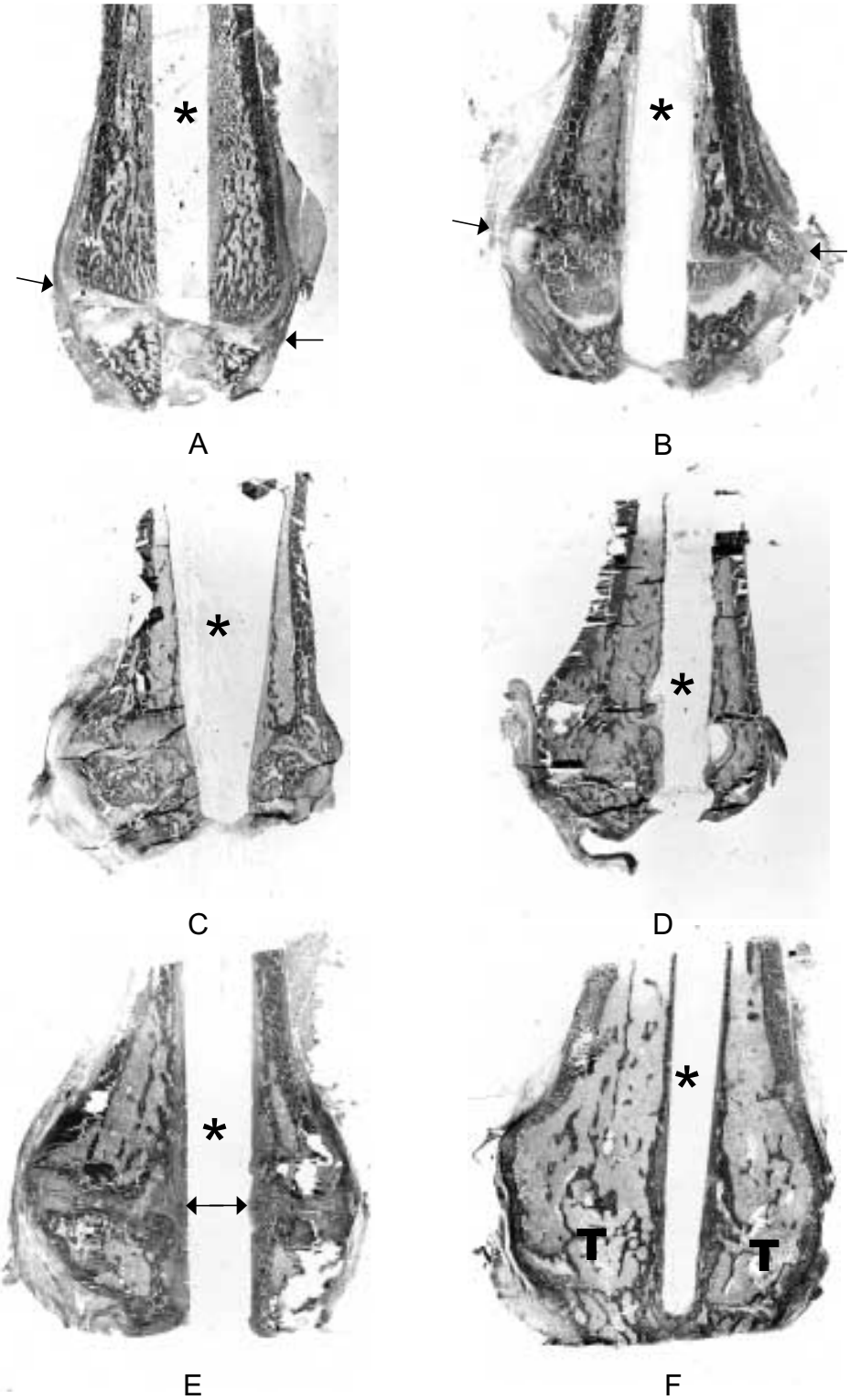
36 weeks. The osteotomy line was not visible in any of the six specimens and only slight new-bone formation was seen. There were some remnants of SR-PGA particles left at the implant site, but the SR-PLLA implant was nearly intact.

48 weeks. The new-bone formation had nearly ceased in both specimens in the microradiographic and oxytetracycline fluorescence studies. There was no birefringent SR-PGA material left in any of the specimens, whereas the gross geometry of the SR-PLLA pin was intact in all specimens.

52 weeks. All of the specimens were consolidated both in the SR-PGA specimens (Fig. 19 F) and in the SR-PLLA specimens (Fig. 20 F), and the osteotomy line was not visible. The SR-PGA pin had degraded totally and was replaced by connective tissue and bone marrow cells. The SR-PLLA implant-tissue border was still distinct.



Figures 19 A-F. Photomicrographs of a coronal section of an osteotomized (black arrows) rat distal femur at a follow-up of 1 (A), 3 (B), 6 (C), 12 (D), 24 (E), and 52 (F) weeks fixed with an SR-PGA pin. An intense new-bone formation can be seen at one week lasting up to 24 weeks. From six weeks on the trabecular bone bridges (T) can be seen. The pin was replaced by connective tissue (C) (Masson-Goldner stain).



Figures 20 A-F.Photomicrographs of a coronal section of an osteotomized (black arrows) rat distal femur at a follow-up of 1 (A), 3 (B), 6 (C), 12 (D), 24 (E), and 52 (F) weeks fixed with an SR-PLLA pin. An intense new-bone formation lasts up to six weeks, and the host tissue responses are quite mild during the whole follow-up time. At 24 weeks there is more connective tissue (two-side black arrows) than before but after that the osteotomy lines are not visible. The pin (black asterisk) is intact during the whole follow-up period. (Masson-Goldner stain).

5.1.2.3. Histomorphometry

A vigorous osteostimulatory tissue response to SR-PGA and SR-PLLA pins was observed at one week after implantation (Fig. 21). This reaction reached its highest value 24 weeks after SR-PGA pin fixation and six weeks after SR-PLLA pin fixation. The highest values of the mean trabecular bone area fraction, 27.9 % for SR-PGA pins and 28.1 % for SR-PLLA pins, were measured at 48 weeks (Fig. 22). At 12 weeks there was a peak of phagocytizing macrophages in the specimens with SR-PGA pin fixation (Fig. 23).

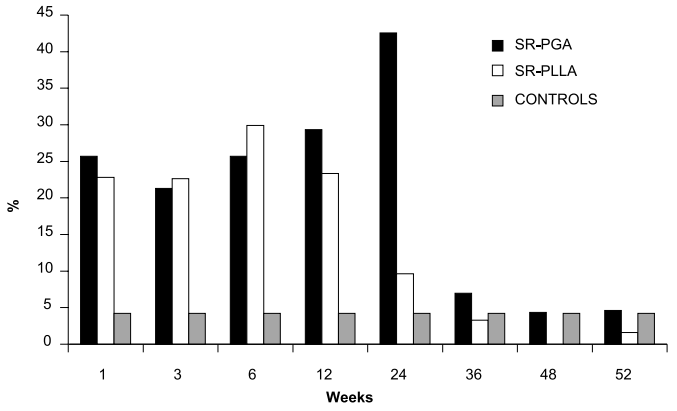
The host tissue responses were more active to polyglycolide pins than to polylevolactide pins. The SR-PGA pins were almost totally degraded by 24 weeks, and the SR-PLLA pins were nearly intact during the whole follow-up of 52 weeks (Fig. 24).

Figure 21. The osteoid formation surface over the total trabecular surface (%) in the same rat osteotomized distal femur at 1, 3, 6, 12, 24, 36, 48, and 52 weeks fixed either with an SR-PGA or SR-PLLA pin. A vigourous osteostimulatory response to both pins was observed at one week. The most active new bone formation was reached at 24 weeks after SR-PGA and at six weeks after SR-PLLA pin fixation. The control value is the mean value of rats killed after each follow-up time.

Figure 22. The total trabecular bone area fraction of the total tissue area (%) in the osteotomized distal femur of the same rat at 1, 3, 6, 12, 24, 36, 48, and 52 weeks after fixation of an SR-PGA and SR-PLLA pin. The highest values of the mean trabecular bone area fraction, 27.9 % for SR-PGA and 28.1 % for SR-PLLA pins, were measured at 48 weeks. The control value is the mean value of rats killed after each follow-up time.

Figure 23. The number of macrophages (M-F) and giant cells (G-C) at the tissue-implant interface (counted per medium power field, x 400) in the same rat osteotomized distal femur at various time points after fixation of an SR-PGA and SR-PLLA pin. At 12 weeks the macrophages reached their highest numbers after SR-PGA-fixed specimens and after that they decreased.

Figure 24. The area occupied by the implant (%) in the osteotomized distal femur of the same rat at 1, 3, 6, 12, 24, 36, 48, and 52 weeks fixed either with an SR-PGA or SR-PLLA pin. The SR-PGA pins were almost degraded by 24 weeks, whereas the SR-PLLA pins showed nearly no degradation during the whole follow-up time.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SR-PGA
SR-PLLA
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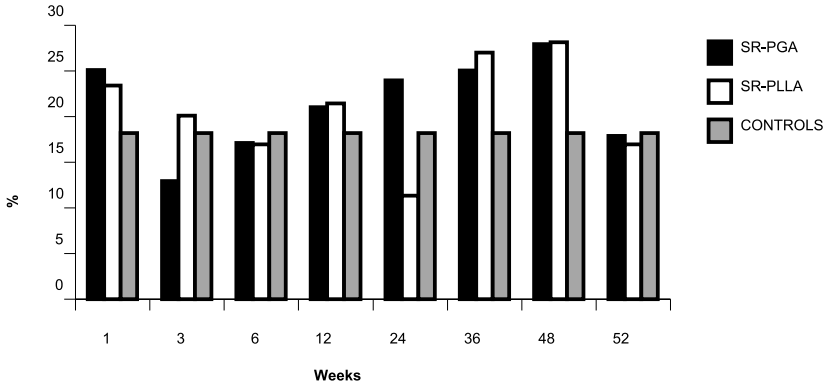
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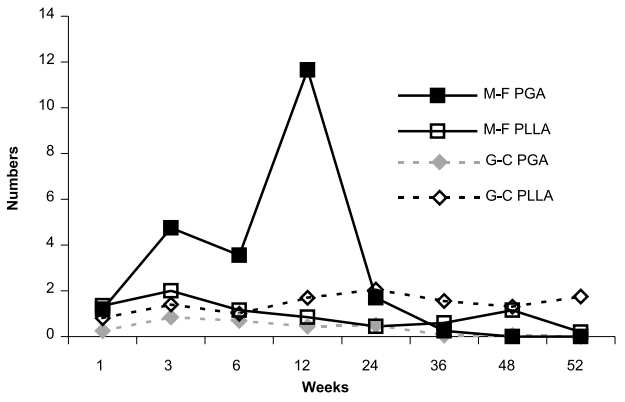
14
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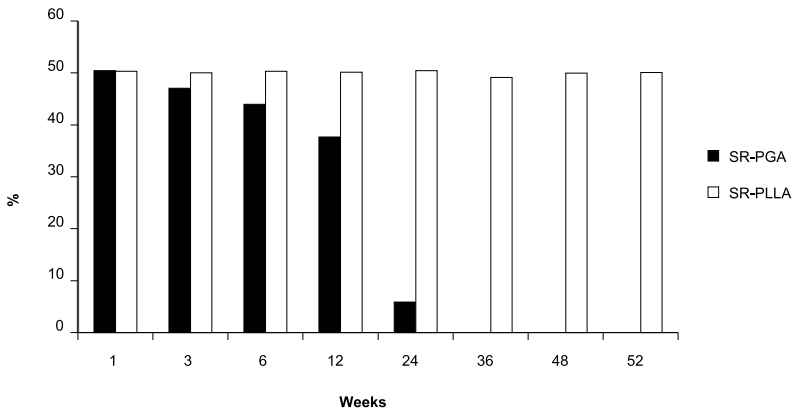
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SR-PGA
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Weeks

Table 2. Results of histomorphometric analysis of the mean values of all follow-up times at the tissue-implant interface after implantation without osteotomy or fixation of osteotomies in the same rat distal femur with self-reinforced polyglycolide (SR-PGA) and self-reinforced poly-levo-lactide (SR-PLLA) pin (mean and SD)

Variables analysed	SR-PGA Mean (SD) mm^2 (mm^2)	SR-PLLA Mean (SD) mm^2 (mm^2)	Together Mean (SD) mm^2 (mm^2)
Study without osteotomy			
Total trabecular bone area	1.12 (0.51)	1.01 (0.32)	1.07 (0.43)[1]
Osteoid surface fraction	0.24 (0.21)[2]	0.16 (0.17)[2]	0.20 (0.20)[3]
Active osteoid formation surface	0.12 (0.13)[4]	0.06 (0.08)[4]	0.09 (0.11)[5]
Implant occupied area	0.05 (0.05)[6]	0.11 (0.00)[6]	0.08 (0.05)
Study with osteotomy			
Total trabecular bone area	0.73 (0.32)	0.72 (0.32)	0.73 (0.32)[1]
Osteoid surface fraction	0.17 (0.15)[7]	0.13 (0.13)[7]	0.15 (0.14)[3]
Active osteoid formation surface	0.07 (0.08)	0.05 (0.07)	0.06 (0.08)[5]
Implant occupied area	0.05 (0.05)[8]	0.12 (0.00)[8]	0.09 (0.05)

SD = standard deviation

[1, 6, 8] $p < 0.001$ (two-way analysis of variance)

[3, 5] $p < 0.05$ (two-way analysis of variance)

[2, 4, 7] $p < 0.01$ (two-way analysis of variance)

Table 3. Results of analysed cells in histomorphometric analysis of the mean of all follow-up times at the tissue-implant interface after implantation without osteotomy or fixation of osteotomies in the same rat distal femur with self-reinforced polyglycolide (SR-PGA) and self-reinforced poly-levo-lactide (SR-PLLA) pin (mean and SD)

Cells analysed	SR-PGA Mean (SD)	SR-PLLA Mean (SD)	Together Mean (SD)
Study without osteotomy			
Osteoblasts	4.9 (5.5)[1]	3.1 (3.6)[1]	4.0 (4.7)[2]
Giant cells	0.7 (0.7)[3]	1.8 (0.8)[3]	1.3 (0.1)[4]
Macrophages	2.4 (5.8)[5]	1.0 (0.9)[5]	1.7 (4.2)
Fibrocytes	1.4 (2.3)[6]	1.0 (2.2)[6]	1.2 (2.2)[7]
Study with osteotomy			
Osteoblasts	2.2 (2.3)[8]	1.8 (2.5)[8]	2.0 (2.4)[2]
Giant cells	0.3 (0.5)[9]	1.4 (0.8)[9]	0.9 (0.9)[4]
Macrophages	2.9 (4.8)[10]	1.0 (0.9)[10]	1.9 (3.6)
Fibrocytes	2.9 (3.7)[11]	5.1 (2.8)[11]	4.0 (3.4)[7]

SD = standard deviation

[2, 3, 4, 5, 7, 9, 10] $p < 0.001$ (two-way analysis of variance)

[1, 6, 8, 11] $p < 0.05$ (two-way analysis ofvariance)

5.1.3. Comments on histologic "meta-analyses"

The comparison of the histologic studies revealed that there were significantly more trabecular bone ($p < 0.001$), osteoid, and active osteoid ($p < 0.05$) in the rat distal femur in the study without osteotomy than in that with osteotomy. Also, there was significantly but somewhat less ($p < 0.01$) osteoid and active osteoid formation in the rat distal femur in the SR-PLLA-fixed specimens than in the SR-PGA-fixed specimens, especially in the study without osteotomy (Table 2).

The number of osteoblasts and giant cells was significantly greater ($p < 0.001$) and the number of fibrocytes significantly smaller ($p < 0.001$) in the rat distal femur in the study without osteotomy than in that with osteotomy. In the SR-PLLA-fixed specimens there were significantly more giant cells ($p < 0.001$) but fewer osteoblasts ($p < 0.05$) and macrophages ($p < 0.001$) than in the SR-PGA-fixed specimens (Table 3).

5.2. STRENGTH STUDIES

5.2.1. Shear-load carrying capacity of cancellous bone after self-reinforced polyglycolic acid (SR-PGA) and self-reinforced poly-L-lactic acid (SR-PLLA) pin implantation in the same rat

The shear-load carrying capacities of the intact bones varied from 63 to 208 N (the mean peak force at failure was 148 N) (Fig. 25). The shear-load carrying capacities stayed nearly at the same level from one to 12 weeks in the SR-PGA-implanted specimens and after that they started to raise reaching their highest value at 36 weeks (218 N), after which they decreased to the level of the control ones. The shear-load carrying capacities reached their highest values at 36 weeks also in the SR-PLLA-implanted (260 N) and control specimens (208 N). At 52 weeks both the SR-PGA (178 N) and control specimens (179 N) had significantly ($p < 0.001$) higher values than the SR-PLLA-implanted specimens (142 N). Otherwise the shear-load carrying capacities showed higher values in the SR-PLLA-implanted specimens. During the whole follow-up period the mean shear-load carrying capacity of the SR-PGA-implanted specimens was 171 N and that of SR-PLLA-implanted specimens 181 N, the corresponding value of the control specimens being 148 N. (Fig. 25).

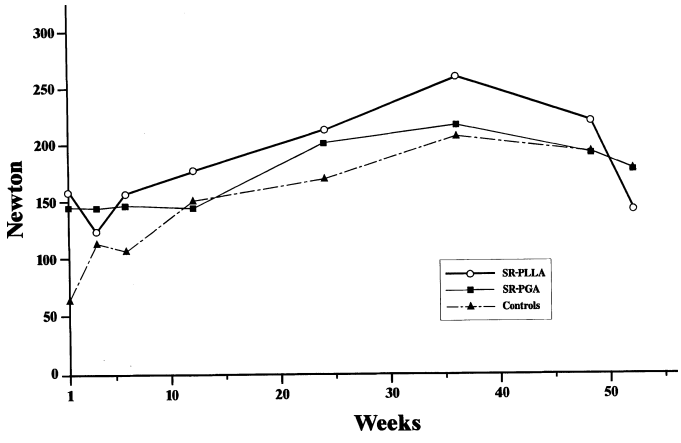

Figure 25. The shear-load carrying capacities (N) of cancellous bone after SR-PGA and SR-PLLA pin implantation in the same rat and of the control intact bones. The shear-load carrying capacities reached their highest values at 36 weeks in all, being 218 N after SR-PGA implanted specimens, 260 N after SR-PLLA pin implantation, and 208 N in the control bones. Thereafter they gradually decreased. During the whole follow-up period the mean shear-load carrying capacity of the SR-PGA-implanted specimens was 171 N and that of SR-PLLA-implanted specimens 181 N, the corresponding value of the control specimens being 148 N.

5.2.2. Shear-load carrying capacity of osteotomized cancellous bone fixed either with self-reinforced polyglycolic acid (SR-PGA) or self-reinforced poly-L-lactic acid (SR-PLLA) pins in the same rat distal femurs

The shear-load carrying capacities reached their highest values in the osteotomized cancellous bones at 24 weeks in the SR-PGA-fixed specimens (286 N), at 52 weeks in the SR-PLLA-fixed specimens (275 N), and at 36 weeks in the control ones (208 N) (Fig. 26). In the SR-PGA-fixed specimens of the osteotomized bones the shear-load carrying capacities rose until 24 weeks and after that decreased, being at the end of the follow-up nearly the same in the SR-PGA-fixed specimens (264 N) and in the SR-PLLA-fixed specimens (275 N), which both are significantly higher ($p < 0.001$) compared to the control bones (178 N). In the SR-PLLA-fixed specimens of the osteotomized bones the strength values of the pins increased after three weeks, but there was a decrease at 24 weeks. After that the shear-load carrying capacities started to rise because of the influence of the healed osteotomy. In the control bones the shear-load carrying capacities were weaker than in the SR-PGA- and SR-PLLA-fixed specimens of the osteotomized bones except at three weeks. During the whole follow-up period the mean shear-load carrying capacity of the SR-PGA-fixed specimens was 199 N and that of the SR-PLLA-fixed specimens 215 N, the corresponding value of the control specimens being 148 N (Fig. 26).

5.2.3. Comments on "meta-analyses" of shear strength studies

The shear-load carrying capacities of the rat distal femur were greater at one and three weeks in the study without osteotomy than in that with osteotomy, as the osteotomy had not yet healed and the implant carried until the bone-implant broke in the strong metaphyseal area. From six weeks on, the shear-load carrying capacities were greater in the study with osteotomy, as the osteotomies were consolidated and the osteostimulatory response had been affected due to bone remodelling so that the bone was also stronger in that study. The SR-PGA implanted specimens had lower shear-load carrying capacities except at three weeks in both studies, because the SR-PLLA implants carried and bent until the specimens

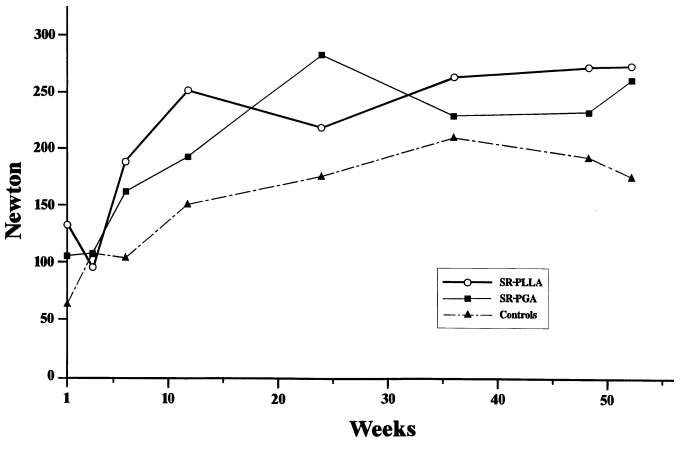

Figure 26. The shear-load carrying capacities (N) of cancellous bone osteotomies fixed either with an SR-PGA or SR-PLLA pin in the same rat distal femur and of the control intact bones. The shear-load carrying capacities reached their highest values at 24 weeks in the SR-PGA-fixed specimens (286 N), at 52 weeks in the SR-PLLA-fixed specimens (275 N), and at 36 weeks in the control bones (208 N). During the whole follow-up period the mean shear-load carrying capacity of the SR-PGA-fixed specimens was 199 N and that of SR-PLLA-fixed specimens 215 N, the corresponding value of the control specimens being 148 N.

broke proximal to the implant, whereas the SR-PGA pins started to lose their strength properties and the specimens broke in the strong cancellous bone.

Also the SR-PGA-fixed osteotomies had significantly higher values than the SR-PLLA-fixed osteotomies at 24 weeks ($p < 0.001$), because the SR-PLLA pins had started to lose their strength properties and did not carry and bend any more. After that the shear-load carrying capacities reached the state where they stayed in both fixed specimens, which was significantly higher than that of the control ones ($p < 0.001$).

6. DISCUSSION

The present study is, to the knowledge of the author, the first report on tissue response and mechanical testing of the shear-load carrying capacities of bioabsorbable implants in the cancellous bone with or without osteotomy in the same animal.

A number of bioabsorbable polymeric implants are used in various biomedical applications (Rokkanen 1998). The elastic modulus of absorbable implants is approximately the same as that of cortical bone, which may allow remodelling to occur at the beginning, as absorbable implants cause normal initial stress to the healing bone. Thus, stress shielding can be avoided (Partio et al. 1992d). However, absorbable implants cannot be used when high mechanical strengths are needed, though self-reinforced (SR-) techniques have made these devices much stronger (Törmälä et al. 1990, 1996, Pohjonen et al. 1997).

Several experimental animal studies have been done on the biocompatibility and strength retention of self-reinforced polyglycolic acid (SR-PGA) (Vainionpää 1987, Vasenius 1990) and self-reinforced polylactic acid (SR-PLLA) (Majola 1992, Manninen 1993a, Pihlajamäki 1994, Jukkala-Partio 1997, Koskikare 1997b). By experimental designs it is possible to minimize the variability of the results as well as to analyse in detail the biocompatibility, bioabsorption, and fixation properties of these two polyester implants. Studies have been performed on rats (Vasenius 1988, Bos et al. 1991, Majola et al. 1991, Ashammakhi et al. 1995a, Viljanen et al. 1997a Tielinen et al. 1999), rabbits (Vainionpää 1986, Vainionpää et al. 1986, Vihtonen et al. 1987, Vasenius et al. 1989, 1990a, 1990b, Böstman et al. 1991, Matsusue et al. 1991, Böstman et al. 1992a, 1992b, 1992d, Majola et al. 1992a, 1992b, Manninen et al. 1992a, 1993, Manninen 1993b, Päivärinta et al. 1993, Pihlajamäki et al. 1994b, 1994c, 1994d, Vasenius et al 1994, Matsusue et al. 1995, Koskikare et al. 1996, 1997a, 1997b, Viljanen et al. 1997b, Puumanen et al. 2000), dogs (Räihä et al. 1990, Miettinen et al. 1992), and sheep (Suuronen et al. 1991, Manninen et al. 1992b, Suuronen et la. 1992, Weiler et al. 1996, Jukkala-Partio et al. 1997, Peltoniemi et al. 1998a, 1998b, 1999a, 1999b). However, there are no studies in which these two polyesters, SR-PGA and SR-PLLA, have been implanted in the same animal to compare them with each other.

The distal rat femur was chosen, because it is principally of cancellous nature and easy to exposure. In the histologic examinations the degradation process of the pin and the tissue response to the polymer could be simultaneously observed. In the biomechanical measurements the shear-load carrying capacities were studied.

In the present study, the biocompatibility of the SR-PGA and SR-PLLA implants was good, and clinically significant foreign-body reactions, such as swelling or infection, did not occur during the one-year follow-up. This is in accordance with earlier literature, as there is only one earlier animal study in which late foreign-body reaction around subcutaneously implanted SR-PLLA plate was reported in one rat followed up for 143 weeks, whereas no reaction was seen in the animals killed up to 104 weeks after implantation (Bos et al. 1991).

Osteoid formation, tissue response and pin degradation

After implantation of the SR-PGA and SR-PLLA pins in the distal femurs of the same rat, the initial phenomena were studied. The operation itself increased the osteostimulatory response in bone because of trauma. Also, both the SR-PGA and SR-PLLA pins seemed to induce an osteostimulatory response around their borders after implantation into cancellous bone. However, the pattern of new-bone formation was different for these two absorbable polyesters, as the highest values of the fractional osteoid surface were reached at one week in the SR-PLLA and SR-PGA-implanted specimens, but most of the host cell activity was seen at six, 12, and 24 weeks in the SR-PGA implanted specimens, being significantly higher compared to the SR-PLLA-implanted specimens, as also a peak number of macrophages was seen at 12 weeks in the SR-PGA-implanted specimens. This is in accordance with Wolff´s law in 1892 which describes the functional remodelling and repair of the bone, as in the present study most trabecular bone was seen at 24 weeks after the most new bone formation and macrophage activation. By 48 weeks the response to the SR-PGA and SR-PLLA implant gradually faded, and there was more total trabecular bone in both implanted specimens than in the control specimens, which could suggest that they have some osteostimulatory response.

To understand better the clinical relevance of the studied two polyesters, transversal transcondylar osteotomies were done in the distal femur of the same rat and fixed with SR-PGA and SR-PLLA pins. Thus, the whole healing process lasted longer than in the study where osteotomy was not done due to the influence of osteotomy trauma and the relative movement at the osteotomy site during healing. In one previous histomorphometric study of the tissue response to PGA screws in the fixation of transcondylar osteotomy of the distal rabbit femur with follow up-times of 20, 40, 80, and 250 days, a vigorous new bone formation was observed as early as one week after implantation being highest at three to six weeks post-implantation. At the same time the mean fractional volume of trabecular bone in the sample fields was threefold when compared with that of the intact control bone. At the end of the follow-up time, the trabecular bone volume had decreased to values of the same magnitude as those of the intact control sides, which indicates that possible osteostimulatory potential of PGA would have been transitory. In another histomorphometric study of SR-PLLA expansion plugs in cancellous bone osteotomies of distal rabbit femurs, the most active osteoblastic response was seen in the three- and six-week specimens, and within the 24-week follow-up time no significant diminution of the osteoid surface fraction was seen, thus showing some osteostimulatory potential. Majola et al. (1991) found in one histomorphometric study on rats that the trabecular bone remained high during a 48-week follow-up time after fixation of transversal distal femoral osteotomies with SR-PLLA or SR-PDLLA screws. In the present study trabecular bone was most prominent at 48 weeks in the SR-PGA- and SR-PLLA-fixed specimens, which indicates that this osteostimulatory response also lasted longer than it did in the study without osteotomy. Also bones that received an implant seemed to show an osteostimulatory response during the consolidation of the osteotomies, as there was far more trabecular bone with the SR-PGA- and SR-PLLA-fixed specimens compared to the control intact bones at 48 weeks.

Bioabsorption of a polymer activates polymorphonuclear leucocytes which are followed by macrophages, giant cells, and large mononuclear cells around the implant. In one earlier study (Päivärinta et al. 1993), in which rabbit transverse distal femoral osteotomies were fixed with SR-PGA or SR-PLLA screws, no difference emerged with giant cells, but the number of macrophages was significantly higher in the six-week and 12-week PGA-fixed samples than in the corresponding

PLLA-fixed samples. In the present histologic studies the number of macrophages was significantly higher at 12 weeks in the SR-PGA-fixed specimens compared to the SR-PLLA-fixed specimens showing the most active degradation and bioabsorption of the SR-PGA pin at that time, as SR-PGA was almost totally degraded by 24 weeks whereas the SR-PLLA pins were biologically fairly inert within the follow-up time of one year and no signs of an inflammatory tissue response were seen.

Shear-load carrying capacities

In the mechanical study of SR-PGA and SR-PLLA pins in the distal femurs of the same rats, the highest shear-load carrying capacities were found in both implanted specimens at 36 weeks, which can be explained by the increasing strength of the bone after the most trabecular bone observed at 24 weeks, but also by the increasing weight of rats and the changes in the bone structure due to the ageing of the rats. Because of the different properties of SR-PGA and SR-PLLA, the present mechanical study was complicated to perform, as SR-PGA started to degrade as early as at three weeks and there was no birefringent material left at 36 weeks, whereas SR-PLLA did not show any signs of degradation at 52 weeks. In the present study the shear-load carrying capacities were bigger in the SR-PLLA-implanted specimens than in the SR-PGA-implanted specimens, except at three weeks, as the SR-PGA-implanted specimens broke in the strong metaphyseal bone area but the SR-PLLA pin carried and bent until the bone-implant broke proximal to the pin and, at 52 weeks, as the influence of the pins had ceased and the SR-PLLA pins did not carry the load any more. It is of importance to know how the studied implants behave *in vivo* conditions to find out whether they can be used in orthopaedics and traumatology.

Majola et al. (1992a) found that, during the shear strength experiment of SR-PLA rods *in vivo*, the rods retained their cross-sectional dimensions. Also, delamination did not contribute to the shear deformation of the rod as long as the still strong PLLA fibres were able to carry most of the shear load. This is a favourable phenomenon considering the clinical application of the SR-PLLA rods, as the shear-load carrying capacity of the rod has an important role in the fixation of cancellous bone fractures and osteotomies (Vainionpää et al. 1989).

After transversal transcodylar osteotomies of the same rat femurs fixed either with SR-PGA or SR-PLLA pins, the shear-load carrying capacities reached their highest values at 24 weeks in the SR-PGA-fixed specimens, at 52 weeks in the SR-PLLA-fixed specimens, and at 36 weeks in the control specimens. The values of the shear-load carrying capacities were affected by several factors, such as the strength retention and degradation time of the pins and the osteostimulatory effects of the healing osteotomized bones. The shear strength of the SR-PGA rod decreases to the level of cancellous bone in four to six weeks in the subcutis of rabbits (Vasenius et al. 1989), and the SR-PLLA rod loses its mechanical properties after 48 weeks (Pohjonen et al. 1989). In one previous study (Manninen 1993b) SR-PLLA rods were studied in the fixation of 42 diaphyseal femoral osteotomies in rabbits to measure the strength of the healing bone and the weakening of the implant. The shear strength decreased significantly between 12 and 24 weeks. Until the 12th week the bone had reached more than 80 % of the shear-load carrying capacities of the intact control bones.

Based on the present study it may be concluded that after the influence of the pins had ceased and the osteotomies consolidated, the shear-load carrying capacities reached their highest values and remained on the level which was higher than that of the control ones, thus showing osteostimulatory effects of the SR-PGA and SR-PLLA pins and healing of the osteotomized bones.

Future research

Although the present findings cannot be directly compared to any actual clinical situation in humans, the results of this study can be used as a basis for further clinical studies. One of the main interests in developing more effective bioabsorbable implants is to find new materials with low tissue response and longer strength retention compared to SR-PGA and faster degradation and higher initial mechanical strength compared to SR-PLLA. Recently it has been also shown that combining transforming growth factor-ß1 to a bioabsorbable SR-PLLA pin (Tielinen et al. 1999) enhances bone formation in the cancellous bone, thus widening the utilizations of bioabsorbable implants. Jukkala-Partio et al. (2000) have fixed impacted or minimally displaced subcapital femoral neck fractures (Garden Stage I and II fractures) and, in younger patients Garden III fractures with SR-PLLA lag screws safely and with favourable results. Also Saikku-Bäckström et al. (2001) have demonstrated promising results when using fibrillated SR-PLA96 rods in the intramedullar fixation of simple cortical bone osteotomies in rabbits. Further research is needed to develop such implants as will fulfill these challenging properties required in the treatment of weight-bearing cortical bone fractures.

7. CONCLUSIONS

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

1. In the intact bone osteostimulatory effect of both SR-PGA and SR-PLLA pins was documented by active new bone formation which was highest one week after SR-PLLA pin implantation and 12 weeks after SR-PGA pin implantation, respectively. Degradation was faster in SR-PGA implanted specimens at 12 weeks indicated by the peak number of phagocytizing macrophages. Most trabecular bone was evident 24 weeks after both SR-PGA and SR-PLLA implantation.

2. In the osteotomized bone the osteostimulatory effect of both SR-PGA and SR-PLLA pins was documented by intensive new bone formation as early as at one week, but it reached its highest value at 24 weeks in the SR-PGA-fixed osteotomies and at six weeks in the SR-PLLA-fixed specimens. Degradation was stimulated in the SR-PGA-fixed specimens at 12 weeks, as there were more phagocytizing macrophages than in the SR-PLLA-fixed specimens. Remodelling of bone was seen as the most trabecular bone at 48 weeks in both specimens.

The patterns of new bone formation were different with these studies, as the whole healing process started later and lasted longer in the osteotomized bone than in the intact bone.

3. In the intact bone the shear-load carrying capacities reached their highest values at 36 weeks in the SR-PGA- and SR-PLLA-implanted specimens and in the control bones after the most trabecular bone measured histomorphometrically at 24 weeks. The values were higher in the SR-PLLA-implanted bone specimens, as the pins carried the load and bent until the bone-implant broke proximal to the implant, except at three weeks when the bone was still strong in the cancellous area in the SR-PGA-implanted specimens and, at 52 weeks, when the molecular weight and strength had clearly decreased but the mass of the PLLA pin was still the same and the pin did not carry any more.

4. In the osteotomized bone the shear-load carrying capacities reached their highest values at 24 weeks in the SR-PGA-fixed specimens, at 52 weeks in the SR-PLLA fixed specimens, and at 36 weeks in the control bones. At the end of the one-year follow-up the values were higher both in the SR-PGA and SR-PLLA-fixed specimens than in control bones. Several factors affected these values, such as the osteostimulatory effects, degradation time and the strength rentention of the pins.

The differences of the values of the shear-load carrying capacities arose following the healing process of osteotomized bones, which started to affect after the osteostimulatory response had faded.

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