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Adverse Tissue Reactions to Bioabsorbable Fixation Devices

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Among 2528 patients operated on using pins, rods, bolts, and screws made of polyglycolic acid or polylactic acid, 108 (4.3%) were affected by a clinically significant local inflammatory, sterile tissue reaction. The three most common indications for the use of these fixation devices were a displaced malleolar fracture, a chevron osteotomy for hallux valgus, and a displaced fracture of the radial head. In 107 patients, the reaction was elicited by a polyglycolic acid implant, and in one patient by a polylactic acid implant. The incidences were 5.3% (107 of 2037) and 0.2% (one of 491), respectively. The adverse tissue responses to polyglycolic acid were seen 11 weeks after the operation, on average, whereas the reaction to polylactic acid occurred 4.3 years after fixation of an ankle fracture. The mild reactions consisted of a painful erythematous papule of a few weeks' duration. Those of medium severity had a sinus that discharged remnants of the implant for up to 6 months. In the patients affected by severe reactions, extensive osteolytic lesions developed at the implant tracks. The histopathologic picture was that of a nonspecific foreign body reaction. In four patients with vigorous reactions, an arthrodesis of the wrist or ankle later was necessary because of severe osteoarthritis. Several markers of increased risk of the occurrence of a foreign body reaction were found. These included a poorly vascularized bone section such as scaphoid, use of a quinone dye as an additive in the polymer, and an implant geometry with large surface area (screw versus pin or rod). For polyglycolic acid implants, the risk of an adverse tissue response in a given clinical situation can be estimated from the findings of this study. For slow degrading polymers like polylactic acid, however, the ultimate biocompatibility still is unsettled, and additional clinical research with long followup is required.

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Within a few years of the clinical introduction of bioabsorbable fracture fixation devices in the mid-1980s, it was recognized that these materials sometimes are associated with a peculiar method specific adverse tissue response that has the characteristics of an inflammatory foreign body reaction.[3,7,11,25,27,33] The first biodegradable synthetic polymers that were used in the manufacturing of fixation devices on a larger scale were based on polyglycolic acid.[6,18,60,67] When using implants made of polyglycolic acid, the foreign body reactions reported usually have emerged 2 to 4 months after the operation as a painful papule or a discharging sinus over the implantation

site.[8,11,20,28,34,38,44,49] During the past 10 years, a few other bioabsorbable materials have been introduced, the most important among these being polylactic acid, a polymer with a considerably longer degradation time than that of polyglycolic acid. However, after 1.5 decades of increasing use of bioabsorbable fixation devices in numerous orthopaedic applications,[1,2,6,12–14,29,32,35,40,50,59,64–66] knowledge of the clinical biocompatibility of these implants still is limited and scattered.

The incidence of foreign body reactions of clinical significance to bioabsorbable orthopaedic implants recorded in the literature shows a remarkable variation, from none to 47%.[21,23] Because of the relatively small number of patients in most of the clinical series so far reported, and because the number of the patients affected by a foreign body reaction often has been too low, no conclusions of the risk factors, the clinical spectrum, and the natural history of these tissue responses have been confirmed. In the present study, the experience of 108 patients with a foreign body reaction to implants made of polyglycolic acid or polylactic acid is presented. A review of the pertinent literature is included.

MATERIALS AND METHODS

This study comprises 2528 patients with various fresh fractures or orthopaedic disorders requiring internal fixation who were treated using bioabsorbable pins, rods, bolts, or screws made of polyglycolic acid or polylactic acid (Bioscience, Tampere, Finland), from 1985 to 1995 at the authors' institution. The viscometric molecular weight distribution of the devices made of polyglycolic acid ranged from 50,000 to 200,000 d. According to the data supplied by the manufacturer, polyglycolic acid fibers were sintered into implants at high temperatures and pressures to accomplish a fibers in matrix texture, known as a self reinforced device structure. From 1985 to 1988, the polyglycolic acid devices contained a green aromatic quinone dye to stain the otherwise pale implants, but from 1989 on, no additives were used. The stereoisomeric form of polylactic acid used in the manufacturing of the devices was polylevolactide. The material was drawn into an orientated fibrillated self reinforced structure. The raw material viscometric average molecular weight of the polylactic acid was 700,000 d. After processing and sterilization of the implants the molecular weight was 50,000 d and the degree of crystallinity 50%. The implants were sterilized by gamma radiation at doses of 25 kGy.

The most common indication for using these devices among the 2037 patients, in whom principally polyglycolic acid implants were used in internal fixation (Table 1), was a displaced malleolar fracture of the ankle (54.7%), followed by a chevron osteotomy of the first metatarsal bone for hallux valgus (11.8%), and a displaced fracture of the radial head (5.5%). In 377 of these 2037 patients, at least one polylactic acid implant was used simultaneously. Polylactic acid devices were used exclusively in 491 patients.

Among the 2528 patients, a clinically significant foreign body reaction was seen in 108 (4.3%). Only reactions manifesting as a painful erythematous papule or, at presentation, as a discharging sinus were included. Painless transient minor swellings without osteolytic findings on radiographs were excluded. Because of the partly experimental nature of this method of fixation, especially during the early years of the 11-year period, the patients were under keen followup. Patients seeking medical attention elsewhere for adverse tissue reactions to the implants usually were referred back to the university department from the offices of practitioners and from the other hospitals of the catchment area.

For the present study, the files of all patients were scrutinized. The patients with and those without a foreign body reaction were analyzed for age, gender, indication for surgery, implant type, polymer volume implanted, presentation of the tissue reaction, clinical course of the lesion, radiographic appearance, and histopathologic findings.

To review the previous literature on bioabsorbable implants, a computer aided literature search of the MEDLINE database was performed using the key words polyglycolic acid, polylactic acid, and bioabsorbable plus all relevant synonyms and subheadings. In the literature, polyglycolic acid and polyglycolide often are used interchangeably, as well as polylactic acid and polylactide. Likewise, the terms absorbable, body absorbable, degradable, biodegradable, resorbable, and bioresorbable are used synonymously with bioabsorbable. Only studies that were concerned with

TABLE 1. Indications for the Use of Bioabsorbable Polyglycolic Acid Implants and the Incidence of Adverse Tissue Reactions

Indication	Number of Patients	Patients With Reaction		Odds Ratio
		Number	%	
Fixation of fresh fracture				
Lateral clavicle	8	1	12.5	2.6
Distal humerus	88	3	3.4	0.6
Olecranon	71	3	4.2	0.8
Radial head	112	2	1.8	0.3
Distal radius	13	1	7.7	1.5
Bones of the hand	47	3	6.4	1.2
Patella	34	1	2.9	0.5
Proximal tibia	23	1	4.3	0.8
Malleolar segment	1115	69	6.2	1.5
Calcaneus	29	3	10.3	2.1
Metatarsal bones	7	1	14.3	3.0
Other fresh fractures	83	—	—	
Ununited scaphoid fracture	20	5	25.0	6.3
Fixation of coracoid process*	27	2	7.4	1.5
Hauser's operation**	11	2	18.2	4.1
Proximal osteotomy of the first metatarsal bone	14	1	7.1	1.4
Chevron osteotomy	241	8	3.3	0.6
Arthrodesis (hand, ankle, or foot)	54	1	1.9	0.3
Other orthopaedic operations	40	—	—	
Total	2037†	107	5.3	

*In Bristow–Latarjet procedure for recurrent dislocation of the shoulder.

**For recurrent dislocation of the patella.

†There were 377 patients with polyglycolic acid and polylactic acid implants used simultaneously in the fixation procedure, but no reactions were seen over the entrance site of the polylactic acid device.

pins, rods, bolts, or screws were included; those studies reporting the use of minor anchors, staples, tacks, cords, or threads were not included.

In the statistical evaluation, Fisher's exact test, the chi square test, and the Mann-Whitney U test were used (level of significance, $p < 0.05$). Odds ratios were calculated and 95% confidence intervals were constructed where appropriate.

RESULTS

Incidence of Reactions and Markers of Increased Risk

There were 107 patients (5.3%) seen with a clinically significant foreign body reaction among the 2037 patients who were treated surgically using polyglycolic acid implants (Table 1), and one (0.2%) among those 491 treated with polylactic acid implants exclusively. At those anatomic sites where reactions occurred, the incidence varied from 1.8% in fractures of the radial head, to 25% in ununited fractures of the scaphoid (Table 1). In malleolar fractures, the most common indication for the use of bioabsorbable implants in this series, the 95% confidence interval calculated for the reaction rate was from 4.9% to 7.8%.

There was no difference in the age, the male to female ratio, or in the polymer volume implanted between the patients with and those without a foreign body reaction (Table 2). The risk of a reaction neither increased nor decreased in the 377 patients treated using polyglycolic acid and polylactic acid implants simultaneously when compared with those

TABLE 2. Characteristics of Patients With and Those Without a Foreign Body Reaction to Bioabsorbable Fixation Implants

Characteristic	Patients With Reaction (n = 108)	Patients Without Reaction (n = 2420)	p Value*	Odds Ratio
Mean age	38.0 ± 15.4	37.1 ± 16.1	0.83	NA
Gender				
Female	66	1332		1.28
Male	42	1088	0.25	0.78
Implant type causing the foreign body reaction				
Pin or rod	50	1387		0.64
Screw or serrated bolt	58	1033	0.03	1.56
Quinone dye in implant				
No	67	1872		0.48
Yes	41	548	< 0.001	2.09
Volume of the polymer				
< 500 mm^3	31	865		0.72
500–1500 mm^3	36	809		1.00
> 1500 mm^3	41	746	0.21	1.37

NA = not applicable.

*Level of significance, $p < 0.05$.

treated with polyglycolic acid devices only ($p = 0.74$). The presence of a quinone dye as an additive in the polymer clearly increased the risk of a reaction ($p < 0.001$; odds ratio 2.1). Also the geometry of the implant influenced the reaction rate, with screws and serrated bolts showing a higher incidence of adverse tissue responses ($p = 0.03$; odds ratio 1.6) than pins and rods (Table 2). These findings statistically remained unchanged when fractures of the ankle were considered separately. The mean polymer volume in the ankle of the patients affected by a reaction, 1443 mm^3, did not differ significantly from that of the patients without a reaction, 1227 mm^3 ($p = 0.12$). For screws in the ankle, the incidence was higher than for the simple cylindrical implants ($p = 0.02$).

Clinical Features, Radiographic, and Histopathologic Findings

Among the patients treated with polyglycolic acid devices, the mean interval between the operation and the first clinical signs of a foreign body reaction was 79 days (range, 38–108 days). The reaction initially presented as a suddenly emerging painful, erythematous, fluctuating papule over the implant track. Unless immediately aspirated or incised, the papule usually burst within a few days and revealed a sinus discharging liquid remnants of the disintegrated implant. The mean duration of the discharge was 6 weeks (range, 2–27 weeks). Bacterial cultures did not show any growth. The lesions were treated by debridement with the patient under local or general anesthesia. In 21 cases (19.4%), inpatient care was required.

Radiographs obtained at the time of the clinical manifestation of the adverse tissue responses showed osteolysis along the implant tracks in 62 patients (57.4%) (Figs 1, 2). The bony architecture at the osteolytic foci radiographically was restored within 1 year unless permanent articular damage had occurred during the acute phase of the reaction. Because of a vigorous reaction and redisplacement of the fracture fragments (Fig 1), excision of the radial head was necessary in one patient. In four patients, the foreign body reaction ultimately resulted in a severe osteoarthritis necessitating

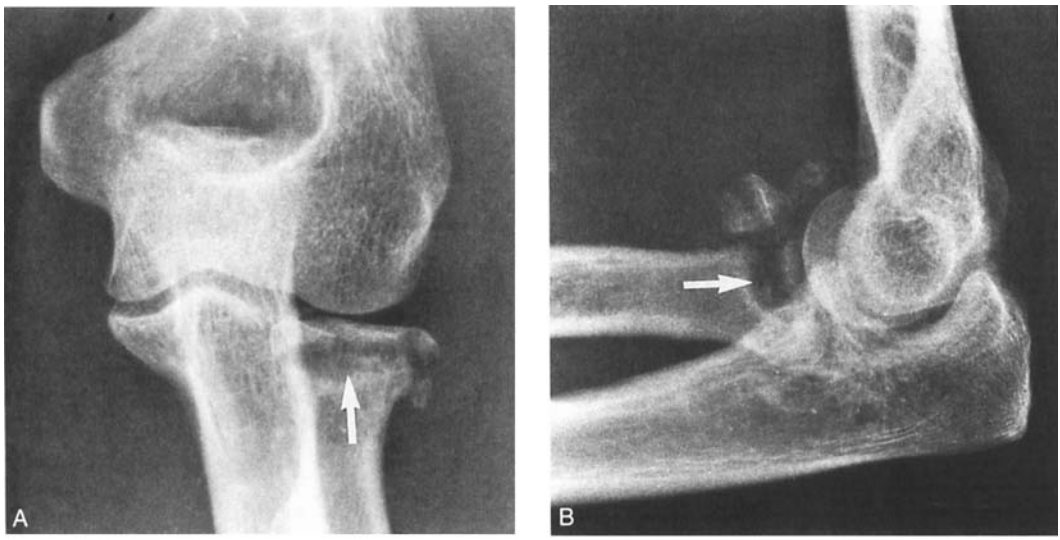

Fig 1A–B. A 36-year-old woman sustained a displaced fracture of the left radial head when she stumbled on some stairs. The fracture was treated by open reduction and internal fixation with two 2.0-mm-diameter polyglycolic acid pins. At 12 weeks, an inflammatory foreign body reaction complicated the course. (A) Anteroposterior radiograph shows an ovoid osteolytic lesion (arrow) in one of the implant tracks. (B) Lateral radiograph shows that the osteolysis (arrow) resulted in redisplacement of the fracture fragments. Resection of the radial head was later necessary.

an arthrodesis procedure, three of which were in the ankle and one was in the radiocarpal joint.

Biopsy specimens showed a uniform histopathologic picture of a nonspecific inflammatory foreign body reaction with numerous polymeric particles, birefringent under polarized light, surrounded by mononuclear phagocytes and multinucleated foreign body giant cells. Polymeric debris having a particle size of 25 μm or more usually was lying extracellularly. Immunohistochemically, T lymphocytes were found to be present. No signs of bacterial infection or malignancy emerged on microscopic examination.

Among the patients treated using implants made of polylactic acid, there was only one (0.2%) unequivocal foreign body reaction. This occurred 4.3 years after fixation of a malleolar fracture. The clinical features and the histologic findings were similar to the reactions seen with polyglycolic acid. No sinus developed. This case history is presented in detail elsewhere.[16] On microscopic examination, abundant polymeric debris still was present in the tissues when a biopsy specimen was obtained 57 months after the fracture fixation procedure. In addition to this foreign body reaction, persisting subcutaneous protruding polylactic acid screw heads had to be removed surgically in three patients 2 to 3 years after fixation of a malleolar fracture with polylactic acid screws.

Compilation of Previous Studies

Adverse tissue responses to fixation implants made of polyglycolic acid have been reported in more than 20 previous studies (Table 3), the incidence varying from 2.0% to 46.7%. The highest reaction rates were found in fractures of the distal radius and in fractures of the ankle.[21,33,38]

In studies concerned with polylactic acid implants, the reaction rate was lower (Table 4). In ½ of the studies, no adverse tissue responses were reported. However, in one study

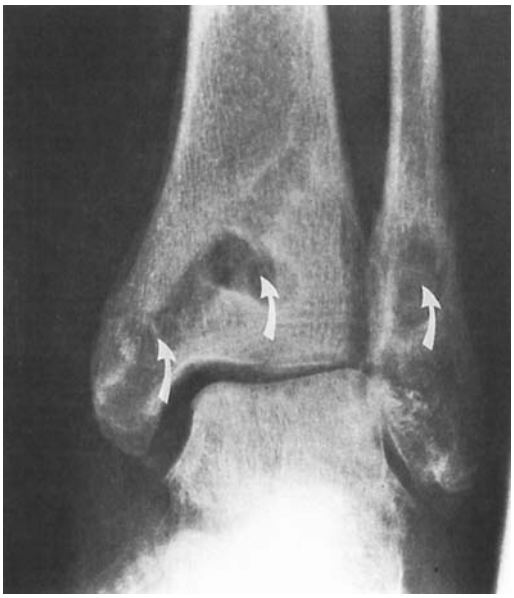

Fig 2. A 47-year-old woman sustained a displaced fracture of the left ankle when she slipped on ice. She was treated with open reduction and internal fixation using polyglycolic acid screws. At 9 weeks, a vigorous sterile foreign body reaction with discharging sinuses on the medial and lateral sides of the ankle emerged. An anteroposterior radiograph shows remarkable osteolytic expansion of all three implant tracks (arrows). The original diameter of the implant tracks, 3.2 mm, has doubled. Severe osteoarthritis of the ankle developed during the following years.

on fractures of the ankle, the reaction rate was 47.4%.[23] The interval between the operations and the clinical signs of the reactions to polylactic acid implants was more than 1 year in all cases recorded.

DISCUSSION

The occurrence of inflammatory foreign body reactions is, along with the relatively high acquisition costs,[9,45] the principal drawback of bioabsorbable fixation devices. In contrast, insufficient mechanical strength, which initially was the main concern for the clinical introduction of these devices, has proved to be a minor problem as long as the implants are used judiciously.[14,18,19,24,30,31,37,39,41,48,51–59,62,63,69]

Even if discussion about the biocompatibility of absorbable materials has focused on polyglycolic acid and polylactic acid, none of the biodegradable polymers suited for manufacturing of absorbable fixation implants appears to be exempt from eliciting adverse tissue responses. Polydioxanone and polyglycolide-co-trimethylene-carbonate have been reported to provoke clinically manifest foreign body reactions.[22,26] In the light of present day knowledge, the fast degrading polymers such as polyglycolic acid are associated with a higher reaction rate than the slow degrading ones like polylactic acid.

Polylactic acid also differs from polyglycolic acid, in addition to its longer degradation time, in that polylactic acid is more hydrophobic because of its methyl groups. The hydrophilic character of polyglycolic acid implants within bone tissue has been shown experimentally.[15,68] When considering the clinical biocompatibility of polylactic acid, polylactic acid was introduced later than polyglycolic acid, and it has been in large scale clinical use for only a few years. Because of its long degradation time, any potential adverse tissue reaction to polylactic acid can be expected to occur up to 4 or 5 years after surgery, as was seen in the present series and in two previous studies regarding the use of polylactic acid plates in maxillofacial surgery.[4,5] Consequently, for the slow degradation stereoisomeric forms of polylactic acid, the true reaction rate cannot be determined yet.

Many extrinsic and intrinsic factors influence the depolymerization behavior of bioabsorbable polymers. Raw materials from different sources often differ considerably from each other in their physicochemical characteristics,[6,17,19,36,43,46,47] which may affect the biocompatibility of the implants manufactured. Such characteristics include molecular weight, thermal history, crystallinity and porosity of the implant, and the presence of residual impurities in the polymer. Unfortunately, the manufacturers seldom are able or willing to supply these data of their products. Yet, the influence of these factors should be recog-

TABLE 3. Clinical Studies Reporting Adverse Tissue Reactions to Fixation Devices Made of Polyglycolic Acid

Study and Year	Number of Patients	Indication for Surgery	Implant Type	Followup Time	Number of Patients with Reaction
Böstman et al[13] (1989)	102	Ankle fractures	Rods*	1 year	2
Hirvensalo[30] (1989)	41	Ankle fractures	Rods	12 to 32 months	6
Böstman et al[11] (1990)	516	Various fractures and orthopedic disorders	Rods	2 to 18 months	41
Hirvensalo et al[31] (1990)	24	Radial head fractures	Pins*	28 months (mean)	2
Barfod and Svendsen[3] (1992)	2	Intraarticular fractures in the knee	Pins	Report of two cases	2
Casteleyn et al[21] (1992)	15	Fractures of distal radius	Rods	1 year	7
Fridén and Rydholm[27] (1992)	1	Osteochondral fragments in the knee	Pins	Case report	1
Frøkjaer and Nue Møller[28] (1992)	25	Ankle fractures	Rods	1 year	1
Hoffman et al[33] (1992)	40	Fractures of distal radius	Pins	2 years	9
Partio et al[52] (1992)	152	Ankle fractures	Screws	19 to 46 months	10
Partio et al[53] (1992)	41	Fractures of olecranon	Rods, screws	12 to 54 months	3
Böstman et al[14] (1993)	71	Pediatric fractures	Pins	3 to 51 months	2
Miketa and Prigoff[49] (1994)	27	Various foot disorders	Pins	Report of two cases	2
Burns[20] (1995)	49	Hallux valgus (osteotomy)	Pins	Minimum 3 months	2
Kankare et al[41] (1995)	16	Ankle fractures	Screws	1 year	3
Pelto-Vasenius et al[55] (1995)	20	Nonunion of scaphoid	Pins	57 to 77 months	5
Hovis and Bucholz[38] (1997)	21	Ankle fractures	Screws	8 to 16 months	8
Kankare[39] (1997)	6	Fractures of tibial condyles	Screws	Minimum 12 months	1
Pelto-Vasenius et al[56] (1997)	70	Hallux valgus (osteotomy)	Pins	1 to 7 years	6
Tuompo et al[66] (1997)	13	Osteochondral fragments in the knee	Pins	1 to 7.6 years	1
Kankare[40] (1998)	25	Fractures of calcaneus	Rods, pins	11 to 38 months	3

*Rods, more than 2 mm in diameter; pins, 2 mm or less in diameter.

TABLE 4. Clinical Studies on the Use of Fixation Devices Made of Polylactic Acid

Study and Year	Number of Patients	Site and Type of Surgery	Implant Type	Followup Time	Comments
Eitenmüller et al[23] (1990)	19	Ankle fractures	Plates and screws	Maximum 3 years	Swelling after 1 year in 9 cases
Partio et al[54] (1992)	7	Subtalar arthrodesis in children	Screws	1 year	
Pihlajamäki et al[57] (1992)	27	Chevron osteotomy, radial head fractures	Pins	8 to 37 months	
Nakamura et al[50] (1993)	28	Acetabular osteotomy	Screws	6 to 24 months	
Niskanen et al[51] (1993)	20	Arthrodesis of first metatarso-phalangeal joint	Pins	Maximum 8 months	Nonunion in 3 cases
Bucholz et al[19] (1994)	83	Medial malleolar fractures	Screws	21 to 59 months	Swelling at 15 months in 1 case
Pihlajamäki et al[58]	33	Bristow–Latarjet procedure for shoulder dislocation	Bolts	6 to 28 months	
Yamamuro et al[69] (1994)	143	Various small fragment fracture, osteotomy, and bone graft fixations	Screws, pins	2 to 6 years	Transient effusion in the knee joint in 1 patient
Barber et al[2] (1995)	42	Anterior cruciate ligament reconstructions	Interference screws	12 to 33 months	
Bergsma et al[4] (1995)	10	Zygomatic fractures	Plates and screws	Minimum 3 years	Late swelling in 4 cases*
Böstman et al[17] (1995)	51	Ankle fractures	Screws	37 to 69 months	Erythema at 22 months in 1 case
Eitenmüller et al[24] (1996)	7	Ankle fractures	Plates and screws	Maximum 2 years	
Matsusue et al[48] (1996)	5	Osteochondral fragments in the knee joint	Pins	2 to 7 years	
Thanner et al[65] (1996)	23	Acetabular cup fixation in hip replacements	Screws	Minimum 2 years	Increased radiolucency at screws

*Four patients sought medical attention for the reaction, and another five showed swelling at a recall.

nized when a comparison of the reaction rate between implants from different sources is attempted. This concerns, above all, implants made of polylactic acid, because there are at least a dozen different manufacturers active within the field. On the other side, the manufacturers of commercially available polyglycolic acid devices are few. The polyglycolic acid implants that were used in this study and in each one of the previous clinical reports referred to in this paper all originate from the same manufacturer.

Although a full blown inflammatory foreign body reaction has a typical clinical picture consisting of local erythema and a discharging sinus, the recognition of an adverse tissue response is not self evident in the mildest cases. This fact could explain some of the variation in the reaction rates reported between different studies in the literature. The mildest reactions lack clinical significance, because they do not increase the morbidity of the patients. In a previous study, the average total costs for a foreign body reaction per patient affected was $1218.[9] The adverse tissue responses encountered in the present study showed a broad, continuous spectrum from nearly subclinical ones to extensive, irreversible tissue damage. Nevertheless, the histopathologic findings were quite uniform, irrespective of the clinical severity of the reaction. Osteolytic lesions were frequent, and when critically located, resulted in a few patients having severe osteoarthritis that later necessitated an arthrodesis procedure. Beside the mechanical joint surface incongruity directly caused by osteolytic foci, it seems possible that the degradation products of polyglycolic acid together with the inflammatory cellular foreign body response exert a detrimental effect on the articular structures.[10] Synovitis is often a conspicuous clinical feature of an acute tissue reaction to bioabsorbable implants.[3,8,11,27,31,38,44,55]

The identification of markers of high risk of a foreign body reaction of clinical significance to bioabsorbable implants in an individual patient is not possible unless the number of patients studied is large enough. No such markers could be found when the first 41 patients with a reaction, who were seen among 516 patients at the authors' department, were analyzed.[11] In the present study, several markers of increased risk emerged. There appeared to be an inverse association between vascularity of the local tissues and reaction rate. Bone sections with a recognizably poor vascularity by nature, such as the scaphoid, showed an over representation of adverse tissue responses. Thus, a sufficient debris clearing capacity of the tissues probably is essential to prevent the accumulation of a local overload of polymeric degradation particles. Unexpectedly, the volume of the implanted polymer as such did not seem to play a decisive role.

An aromatic quinone dye that was used from 1985 to 1988 to color the implants significantly increased the reaction rate. This may apply to any additives and impurities within the polymer. Another finding was that screws were more prone than simple cylindrical pins and rods to evoke reactions. A large surface area of the implant in direct contact with the host tissues increased the cellular reactivity. The crevices associated with an implant having a screw profile also could represent locations in the tissues where an adverse cellular incubation process is possible. The finding would speak in favor of the use of implants with a cylindrical design instead of a screw whenever the clinical application allows.

Foreign body reactions to bioabsorbable polymers obviously represent an inherent biologic tissue response to the degradation and absorption processes of these materials.[7,11,26,38,49,61] Recently, it has been shown that foreign body reactions to biodegradable biomaterials in the rat can be modulated by impregnating the implant with an antibody against a macrophage activating T cell derived cytokine.[42] Although the reaction rate possibly may be decreased by gradually increasing knowledge of the biology of these tissue responses in the future, today the occurrence of adverse tissue reactions appears to be the price

that the patient and the orthopaedic surgeon have to pay for the indisputable advantages of using bioabsorbable fixation devices. Only by being able to predict the risk of a reaction in a given clinical situation can the orthopaedic surgeon weigh the advantages and disadvantages of using bioabsorbable devices against those of metallic fixation in a rational way. The patient material of the present study was large enough to give an estimate of the risk of a reaction at different anatomic sites and with different implant types.

Implants made of polyglycolic acid have a relatively high, although variable, rate of adverse tissue responses. The risk of such reactions seems to be low when using slow degrading polylactic acid devices. However, a long degradation time of several years may be a disadvantage in some clinical situations, because the implant can behave like a metallic implant. Future preclinical and clinical research should not overlook the potential of bioabsorbable materials with degradation times of medium length. Moreover, expanding clinical applications of bioabsorbable implants for use in vascular, urologic, and abdominal surgery may, in time, be able to provide valuable supplementary data on the biocompatibility of these polymers.

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