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Satu Länsman

EVALUATION OF BIOABSORBABLE POLY-L/D-LACTIDE IMPLANT FOR SCLERAL BUCKLING

AN EXPERIMENTAL STUDY

FACULTY OF MEDICINE,
INSTITUTE OF CLINICAL MEDICINE,
DEPARTMENT OF OPHTHALMOLOGY,
UNIVERSITY OF OULU;
DEPARTMENT OF BIOMEDICAL ENGINEERING,
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An experimental study

Academic dissertation to be presented with the assent of the Faculty of Medicine of the University of Oulu for public defence in Auditorium 5 of Oulu University Hospital, on 11 December 2009, at 12 noon

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Abstract

Bioabsorbable materials enable temporary implantation without the need for subsequent implant removal. The aim of the present experimental study was to evaluate the suitability of a fibrous bioabsorbable implant made of poly-L/D-lactide (PLDLA) 96/4 fibres as an episcleral implant.

The general tissue reactions were evaluated in subcutaneous tissues in rats in follow-up periods ranging from 3 days to 48 weeks. The episcleral tissue reactions were studied in rabbits with follow-up periods of one, three, five and 48 weeks. A silicone sponge implant was used as a control material and operations were performed using similar technique with both implants. Tissue reactions were located just around the implant area and consisted of an acute inflammatory reaction in the early follow-up periods, continuing as a foreign body inflammatory reaction. With episcleral implants there were no inflammatory cells seen within the sclera or in the retinal layers, and the structure of the retina and the cornea was also normal. The biocompatibility was good in the 48 week follow-up despite the relatively high surface area of the fibrous implant. The material had not degraded by 48 weeks.

The indentation effect by the PLDLA implant (diameter of 3–3.5mm) was lower than that achieved with the silicone sponge implant (diameter 4mm). The depth of indentation decreased over time in both groups with comparable rates over the follow-up period of 5 months. The duration of the indentation effect was sufficient to be used for scleral buckling in retinal detachment surgery.

In conclusion, the biocompatibility of a fibrous implant made of PLDLA 96/4 placed subcutaneously and episclerally was good in the follow-up lasting 48 weeks despite the relatively high surface area of the implant. The fibrous implant made of PLDLA 96/4 seemed to be well-tolerated by ocular tissues and the indentation effect was sufficiently long.

Keywords: absorbable, episcleral, scleral buckling, tissue reactions

To my dear family

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Oulu, November 2009 Satu Länsman

Abbreviations

e-PTFE	expanded polytetrafluoroethylene
FESEM	field emission scanning electron microscopy
HE	hematoxylin-eosin
kGy	kilogray
Mpa	megapascal
MRad	megarad (rad =radiation absorbed dose)
PBS	phosphate buffered saline
PDS	polydioxanone
PG910	polyglactin; polylactide 90%, polyglycolide 10%
PGA	polyglycolide
PLA	polylactic acid, polylactide
PLA96	poly-L-lactide 96%, poly-D-lactide 4%
PLDLA 96/4	poly-L-lactide 96%, poly-D-lactide 4% (= 92% L- and 8% DL-lactide)
PLDLA	poly-LD-lactide
PLGA 70/30	polylactide 70%, polyglycolide 30%
PLGA	polylactide-polyglycolide
PVR	proliferative vitreoretinopathy
RD	retinal detachment
RPE	retinal pigment epithelium
RRD	rhegmatogenous retinal detachment
s.c.	subcutaneous
SD	standard deviation
SR	self-reinforced
SR-PLDLA	self-reinforced poly-LD-lactide
Tg	glass transition temperature

List of Original Publications

This thesis is based on following articles, which are referred in the text by their Roman numbers:

I Länsman S, Pääkkö P, Ryhänen J, Kellomäki M, Waris E, Törmälä P, Waris T & Ashammakhi N (2006) Poly-L/D-lactide (PLDLA) 96/4 Fibrous Implants: Histological Evaluation in the Subcutis of Experimental Design. J Craniofac Surg 17: 1121–1128.

II Länsman SM, Ellä V, Pääkkö P, Ryhänen J, Kellomäki M, Törmälä P, Waris T & Ashammakhi N Tissue compatibility of knitted biodegradable PLDLA 96/4 cerclage implanted subcutaneously in rats. J Craniofac Surg. Manuscript.

III Länsman SM, Karttunen AI, Hirvelä HK, Palosaari JT, Kellomäki M, Ellä V, Ohtonen PP, Törmälä P, Waris TH & Ashammakhi NA (2005) Persistence of indentation with bioabsorbable poly-L/D-lactide versus silicone sponge scleral buckling implants. Retina 25: 581–586.

IV Länsman S, Pääkkö P, Ryhänen J, Hirvelä H, Kellomäki M, Ellä V, Törmälä P, Waris T & Ashammahki N (2005) Histologic analysis of bioabsorbable scleral buckling implants: an experimental study on rabbits. Retina 25: 1032–1038.

Contents

1 Introduction

Retinal detachment (RD) is a serious pathological condition which may lead to total loss of vision of the affected eye if left untreated. Minor local detachment is often treated with laser coagulation to prevent enlargement. Larger RD is treated surgically, with the aim being to attach the retina to the choroid. Implants can be used as supporting elements, keeping the layers of retina and choroid attached to each other until the healing process accompanied with scarring has taken place, ensuring that the layers remain tightly attached thereafter. In many cases the implant used for this purpose could be temporary.

An increasing number of materials are used in surgical treatment today. Bioabsorbable materials can be synthetic or natural materials that are intended to be degraded and absorbed in the body during a predictable time period. Research on biomaterials has been active, with the emergence not only of new materials and manufacturing techniques, but also providing increasing information about tissue reactions to foreign materials in the body. Different bioabsorbable materials require different time periods for degradation, making it possible to match the mechanical support and bioabsortion of the implant to the healing processes of the operated site and the underlying pathological condition. It is possible to create bioabsorbable materials which have both high mechanical strength and slow degradation rates, which means that there is a gradual loss of support, and therefore the mechanical load does not change abruptly to the surrounding tissues (Törmälä *et al.* 1998).

The first bioabsorbable materials used in surgical treatments in ophthalmology were natural-based materials, for example donor sclera, donor or autologous fascia or animal-derived denatured collagen (gelatin). However, natural materials suffer from several disadvantages e.g. problems related to availability, mechanical weakness and variability in degradation period. There is also the possibility of encountering slow viral infections and immunological problems and thus, as a way of avoiding these problems, research on synthetic bioabsorbable materials has been active. The first report of synthetic bioabsorbable material as a surgical application was written by Kulkarni and his co-workers, who manufactured sutures made of polylactic acid (PLA) (Kulkarni *et al.* 1966). The first commercially available synthetic bioabsorbable suture was a polyglycolide (PGA) suture which was marketed in 1970 (Dexon®). The initial experimental studies on solid implants examined PLA and PGA. The mechanical strength of bioabsorbable implants could be greatly enhanced by the self-

reinforcing method (SR), which has lead to the invention of numerous solid implants, such as plates, rods, screws and stents (Törmälä 1992, Ashammakhi *et al.* 2001, Peltoniemi *et al.* 2002).

Since the need for scleral buckling is only temporary in many cases of RD, synthetic bioabsorbable materials could be a useful alternative and with temporary implants the long-term complications can be avoided. The purpose of the present study was to evaluate the suitability of fibrous implant made of poly-L/D-lactide 96/4 for the treatment of retinal detachment.

2 Review of literature

2.1 Anatomy of the posterior eye

The sclera is an opaque, semi-rigid and stable structure of connective tissue, which provides mechanical support and protection for intraocular tissues. Although the sclera is only semi-rigid, the shape of the eye remains relatively constant due to the intraocular pressure. Choroid is a vascularized tissue which is attached to sclera on its outer side, and to retinal pigment epithelium (RPE) on the inner side. The choroid nourishes the whole RPE as well as the outer layers of retina. RPE has an important role in the process of photoreceptor renewal, accomplished by phagocytosis of the outer segment of photoreceptors. The outer blood-retina-barrier is formed by tight connections between pigment epithelial cells.

The retina is a multi-layered tissue that lines the inner eye wall and is responsible for vision. Histologically, the retina can be divided into nine layers; photoreceptor layer, external limiting membrane, outer nuclear layer, outer plexiform layer, inner nuclear layer, inner plexiform layer, ganglion cell layer, nerve fiber layer and internal limiting membrane. The light is first absorbed by photoreceptors, then converted to an electrochemical event and transferred through the neural retinal cells to the optic nerve. The optic nerve is part of the central nervous system, transmitting impulses to the visual cortex in the brain.

The visual function of the retina is attributable to the photoreceptors, rods and cones. The rods are responsible for vision in darkness and low illumination while cones act in bright light. Unlike rods, the cones are also colour sensitive. The number of cones increases towards the macula which is located in the optical axis of the globe. The fovea is in the middle of macula where only cones are present and in the center of fovea one can find the foveola which is responsible for the highest visual acuity and can be considered to be the most important area of the eye fundus. In the foveola, the whole retinal structure is different from other parts of retina since inner nuclear cell layer and ganglion cell layer are absent and there are no blood vessels and the density of cones is very high.

The vitreous is a transparent gel-like structure consisting of water (over 98%), glycosaminoglycans (mainly hyaluronan) and collagens (mainly type II collagen) (Sebag 1987). In addition, small amounts of other non-collagenous proteins have been found, such as fibrillin, opticin, amino acids and ascorbic acid. Hyaluronan

is a hydrophilic molecule which is highly turgescent and its degree of hydration may vary. It keeps collagen fibres separated from each other thus preventing the collagen filaments from cross-linking and undergoing subsequent aggregation. Collagen fibres are randomly oriented single fibers which are macroscopically invisible. It is the separation of collagen fibres from each other by hyaluronan which ensures the transparency of the vitreous (Sebag & Balazs 1989). The cells within the vitreous are mainly hyalocytes, which not only make hyaluronan but are able to synthesize collagen and they can also phagocytose, migrate and proliferate. The attachments from vitreous to surrounding tissues are variable in their degrees of tightness of adherence, being highest in the anterior part of the retina and pars plana, which is called the vitreous base. There are also other parts of eye with relatively firm attachments, such as around the optic nerve head margins, the lens, retinal blood vessels, at the fovea and for example around retinal scars and degenerative lattice lesions. Age-related changes occur in the vitreous including aggregation of the collagen fibres into thicker bundles, which eventually may become macroscopically visible (Sebag & Balazs 1989). This process is called liquefaction, since the hyaluronan molecules that were previously located around collagen fibres become dissociated and found as adjacent liquid lacunae. These changes increase with age, such that by the age of 80, more than 50% of vitreous is liquid (Sebag & Balazs 1989). These changes evoke a decrease of the shock-absorbing function of the vitreous.

Posterior vitreous detachment means separation of posterior vitreous cortex from the internal limiting membrane of the retina. This is a common phenomenon, occurring in over 60% of people by 75 years of age (Foos 1972). As a result, the vitreous collapses. Posterior vitreous detachment may be non-symptomatic, but can often be sensed as visions of floating objects (floaters) or light flashes. Floaters are caused by aggregated vitreous fibres or glial tissue from optic nerve head margins. The light flashes are due to traction sensed by retina and are attributable to the vitreous fibres during the process of vitreous detachment. The posterior vitreous detachment may continue all the way to the vitreous base, or it may be partial (Foos 1972). The vitreous detachment does not occur at the vitreous base due to the tight attachments in this area.

2.2 Retinal detachment

Retinal detachment is a condition where the neural layer of retina becomes separated from RPE. Any fluid located between the neural retina and RPE is

called subretinal fluid. Subretinal fluid impairs the nutrition of the outer retina, leading to atrophy of the photoreceptors within weeks (Wilson & Green 1987, Berglin *et al.* 1993). In fact, an experimental study in cats found that loss of photoreceptor cells begins within hours, leading to significant decrease of photoreceptor cells within 30 days and causing the loss of 80% of cells in 90 days (Erickson *et al.* 1983). Retinal detachments can be divided according to their pathogenic mechanism to rhegmatogenous, tractional or exudative detachments, or their combination. In rhegmatogenous retinal detachment (RRD), fluid in the subretinal space has entered from the vitreous cavity through a full-thickness retinal break. The two latter groups do not display breaks in the retina. In tractional retinal detachment, the retina is lifted up mechanically due to tractional forces caused by contraction of vitreoretinal membranes. Exudative retinal detachment is caused by the leakage of fluids from vessels, as can occur in some inflammatory diseases (American Academy of Ophthalmology 1996).

Retinal breaks can be either holes or tears. A special group of tears are dialyses, retinal breaks located in the ora serrata, which are often caused by blunt trauma. Not all retinal breaks develop into retinal detachment, since retinal breaks have been found in 5–7% of population but the annual incidence of retinal detachment is only about 6.9 - 12.4 /100 000 (or 0.0069 - 0.0124%) (Haimann *et al*. 1982, Laatikainen *et al*. 1985b, Törnquist *et al*. 1987, Hilton *et al*. 1995). There are several factors that can prevent retinal detachment, such as intraocular pressure, the presence of adhesive-like mucopolysaccharide between pigment epitheliual cells and photoreceptors, continuous phagocytosis and metabolic activity of the pigment epithelial cells and a difference in oncotic pressure between choroid and subretinal space (Ghazi *et al*. 2002, Wilkinson 2004).

Retinal detachment occurs usually in middle-aged or elderly subjects, aged between 40–80 years. There is an increased risk in patients with myopia, lattice degeneration, aphakia or pseudophakia (Laatikainen & Tolppanen 1985, American Academy of Ophthalmology 1996). Acute retinal necrosis, regressed retinopathy of prematurity and ocular trauma are independent risk factors for retinal detachment (Wilkinson 2004).

Most retinal breaks are located in the areas from ora serrata to the equator and only 15% occur posterior to the equator. Since retinal breaks are often caused by tractional forces during posterior vitreous detachment, they are more commonly located in the superior fundus of the eye due to gravitational forces (Laatikainen & Tolppanen 1985). The posterior vitreous detachment may cause problems especially in areas where attachment is tight, such as those occurring around

lattice degeneration lesions. The tractional forces at those areas may cause retinal breaks, creating a route from the vitreous cavity to the subretinal space.

The symptoms of RRD can include photopsia, seeing tiny floaters, decrease in visual acuity or loss of visual field. Photopsia is caused by traction of the retina, most commonly seen in the temporal visual field. The appearance of floating objects may be due to the pigment epithelial cells, collapsed vitreous, glial cells (from margins of optic nerve head) or blood in the vitreous cavity. Decreased visual acuity may be caused by the presence of blood in the vitreous or detachment of the fovea. Visual field loss is often sensed when the detachment has already proceeded to the posterior segment of the eye. Detachment of the macula often leads to poor visual prognosis. Small detachments caused by atrophic holes can be asymptomatic and even heal spontaneously (Brod & Flynn 1996). If spontaneous healing does not occur, the subretinal fluid accumulation increases, evoking an enlargement of the detachment. Since subretinal fluid can be absorbed by RPE cells, continuous liquid flow from the vitreous cavity is necessary for maintenance and extension of the detachment (Wilkinson 2004). The liquid flow is accelerated by rotatory eye movements. Gravity also affects the flow of liquids, causing enlargement of the detachment in a downward direction, i.e. vertical enlargement from the superior temporal quadrant to the inferior temporal quadrant of the retina.

The natural course of retinal detachment may vary greatly, from asymptomatic self-healing local detachments to a rapidly occurring total detachment with a large retinal break. The outcome of operatively treated RRD can be assessed in 2 ways; by anatomic success rate (anatomical reattachment of the retina) and functional success rate (visual acuity). Anatomic success is achieved when the retina is reattached at least on the posterior pole (on the posterior side of supporting implants), with modern techniques this occurs in about 90% or more cases with one or more operations (Laatikainen *et al*. 1985a, Törnquist *et al*. 1988, American Academy of Ophthalmology 1996, Greven *et al*. 1999, Lincoff & Kreissig 2000). The most important issue affecting the prognosis of visual acuity is the preoperative situation of the foveola. If the detachment includes foveola, despite a good postoperative anatomical result, the possibility of achieving the best corrected visual acuity of 20/50 is about 20–37%, though if the foveola remains attached, then the chance for visual acuity of 20/50 or better inreases to about 85% (American Academy of Ophthalmology 1996).

The experimental study of Anderson *et al*., observed that the ultrastructure of photoreceptors and RPE cells did not return to the state it was before detachment

and that the morphological recovery was better when the duration of the detachment was less than one month (Anderson *et al*. 1986). In human post mortem samples, epiretinal membranes were found in 75%, photoreceptor atrophy was seen in 26% and cystoid macular edema in 10% of the patients (Wilson & Green 1987).

The most common reason for anatomical failure of reattachment is proliferative vitreoretinopathy (PVR). This is due to the formation of membranes which can occur on both sides of the detached retina and even within the vitreous. Contraction of these membranes causes tractional forces towards the retina, thus preventing reattachment. Already attached retinal areas may redetach due to the forces of contracting membranes. These membranes are formed by proliferating cells that have migrated and become attached to the retina. The cells that have been found include RPE cells, fibroblasts, macrophages and glial cells. The most important cell type is the RPE cell, which gains access to the vitreous cavity through the retinal break(s). In addition, cryotherapy may allow access of RPE cells to the vitreous cavity, possibly due to tissue damage. These cells are able to attach, proliferate and even change morphologically into fibroblast-like cells producing for example type IV collagen, tenascin and fibronectin (Ioachim *et al*. 2005). The membranes increase in size and thickness by time, making operative reattachment of the retina more challenging or even impossible. In surgical treatment, it is important not only to close all breaks, but also to relieve retinal tractions and to prevent the formation of new tractions. Relief can be achieved for example by peeling the membranes through the intravitreous route or segmenting them after vitrectomy. Intravitreal silicone oil has also been used for reattaching and as internal support for maintaining the attachment of the retina in severe cases. However, in milder cases of PVR, less invasive methods can be sufficient, such as external support with implants. PVR actually causes shrinking of the retina, making the surface area of the retina smaller than the surface area of the underlying choroid and the inner eye wall. Implants are able to decrease tractions by decreasing the circumference of the eye wall. Local support to areas of retinal breaks or PVR folds can be achieved by scleral buckles, while cerclage provides lower indentation in a circumferential fashion. In cases of moderate or severe PVR, supporting implants may be needed permanently due to the shrinkage of the retina.

2.3 Historical review of developments in retinal detachment surgery

2.3.1 Early methods

Retinal detachment was described by de St. Yves in 1722, and the first retinal breaks were seen in 1853 by Coccius. However, initially retinal breaks were thought to be a consequence of retinal detachment, not to be its reason. Gonin introduced the hypothesis of the pathogenesis of rhegmatogenous retinal detachment as it is known today (Gonin 1934, Norton 1975, Lincoff & Kreissig 2000). Since the pathogenesis was unclear, early treatment methods for retinal detachment did not attempt to close retinal breaks. In fact, immobilization in bedrest was recommended, with or without a bandage over the eyes as a way of increasing intraocular pressure. To achieve absorption of subretinal fluid, several non-specific methods like dietary changes, radiotherapy, venesection and various drugs were recommended (Schepens 1983, Michels *et al*. 1990).

Operative methods, such as sclerotomy for releasing subretinal fluid (done already at 1805 by Ware), and perforation of the retina aiming at releasing subretinal fluid to the vitreous cavity were attempted. Even prior to discovering pathogenesis of retinal detachment, chorioretinal adhesions were created to reattach the layers. Adhesion by inflammatory response was first caused by injecting iodine solution subretinally. Later, the inflammatory reaction was achieved by perforating galvanocautery and electrolysis. Diathermy, both perforating and non-perforating was used, but these techniques were replaced by cryotherapy in 1965 (Lincoff *et al.* 1965).

Early methods included also injections of various substances such as saline, serum, rabbit vitreous or aqueous subconjunctivally and intravitreally. The intravitreal injection was thought to have several effects for example dissolving traction bands, causing non-specific stimulation or having an osmotic effect. Also air and gas injections were performed. Suturing the retina with catgut or silk was also done and because it was thought that retinal detachment was caused by globe distension causing stretching of the retina, surgical interventions attempted to decrease the intraocular volume. For example resections of sclera (full-thickness or lamellar) were undertaken aiming to reduce the volume. The results of these procedures were poor (Schepens 1983, Michels *et al.* 1990).

2.3.2 Methods aiming at closing retinal breaks

The first successful surgical treatment aiming at closing retinal breaks was described by Gonin (Gonin 1934). The sealing was achieved by diathermy around the retinal breaks. The retina was appositioned by subretinal fluid release through sclerotomy. Since sealing of the retinal break was considered important, cautery was applied even through the sclerotomy during the operation.

With the appreciation of the importance of retinal breaks, operations for scleral resections (full-thickness or lamellar) and scleral infolding or outfolding were performed aiming at reducing tractional forces. In addition, injections to suprachoroidal space, and shrinking of sclera by diathermy were performed. All these procedures were performed in an attempt to reduce the total volume of the eye or for shortening the sclera. In fact, the infolding operation may actually cause low indentation, but at that time creating an indentation was not the goal of the operation. The infolding operations were placed so that it was easy for the surgeon without any attention being paid to the localisation of retinal breaks (Norton 1975).

The first scleral buckling was conducted in 1937 by Jess, when he used a cotton swab to cause an indentation for 14 days, though the indentation was not intended to attach the retina, but as a way of preventing retinal folds (Jess 1937). Custodis performed the first scleral buckling operation aiming at creating local indentation using Polyviol (a combination of polyvinyl alcohol and Congo red) (Custodis 1952). Thereafter, several materials have been studied and used for scleral buckling; both non-absorbable and absorbable materials (see Chapter 2.5). A temporary indentation was even achieved with an inflatable silicone balloon, which was placed peribulbarly for 1–2 weeks (Kreissig *et al.* 1989).

In addition to the buckling procedure, other operative methods have been developed for more complicated cases, such as vitrectomy, with or without vitreous filling by liquids (heavy or light) or gas. During vitrectomy, peeling of fibrous tissues or retinotomies can be performed. Another method is pneumatic retinopexy, which involves injection of a gas bubble into the vitreous cavity, aiming at closing retinal break due to the local pressure of the bubble. Injecting of biological or synthetic material into the suprachoroidal (subscleral) space has also been tested. This kind of method does not change the shape of bulbus outwards, but it separates choroid from sclera and reduces vitreous space. Suprachoroidally air, blood plasma, autologous homogenized fat, sodium hyaluronate and hydrophilic urethane based polymer have been tested (Smith 1952, Sachsenweger

& Hartwig 1975, Poole & Sudarsky 1986, Mittl & Tiwari 1987, Foulds *et al.* 1988, Schepens & Acosta 1991). However, severe complications may occur due to the injection or insertion itself. Tacks for mechanical fixation of the retina to underlying tissues have also been studied (Abrams *et al.* 1986, Puustjärvi & Teräsvirta 2001).

2.3.3 Current methods for treating retinal detachment

Treatments of retinal detachment aim either at preventing further enlargement of the detached area or to reattaching the retina to the underlying RPE. The first option, preventing further enlargement without reattaching an already detached retina, is used mainly for small localised detachments without significant PVR formation. For operative treatment of RRDs, there are three kinds of surgical approaches in general clinical use: the scleral buckling procedure with or without cerclage, vitrectomy with or without vitreous fillings and pneumatic retinopexy. These methods can also be used in combination either already at the primary operation or during the reoperation if necessary. The method to be used is chosen mainly by the clinical situation, which is mostly dependent on the degree of PVR formation and the localisation of retinal break(s). Since the retinal break is the essential feature of retinal detachment, all procedures involve careful examination and localisation of retinal breaks. In fact, failing in the localisation and closing of all retinal breaks is along with PVR formation, the most common reason for failure in reattaching the retina. (American Academy of Ophthalmology 1996, Wilkinson 2004.)

The external support via a scleral buckle and/or cerclage means that the area of the retinal break is supported with a scleral buckle (also called as segmental buckle or segmental element) from outside of the sclera. Also cerclage (an encircling implant or encircling element) can be used with or without scleral buckling implants. The areas of retinal breaks are treated with a cryoprobe or laser to achieve local scar formation in order to keep the retina attached to the pigment epithelial layer. The implant can be placed episclerally or intrasclerally to create a buckling effect (also called as indentation), which apposes the retina to the underlying RPE and choroid. It is important that the retinal break(s) is sealed during the operation in order to stop the passage of fluid from the vitreous cavity into the subretinal space. The subretinal fluid usually resolves spontaneously with time, but drainage can also be done during the procedure.

Pars plana vitrectomy means that the vitreous is removed by a vitreous cutter through small incisions (sclerotomy) via the pars plana. Several microsurgical methods, for example excision or cutting of tractional bands and filling the vitreous cavity with air, gas or silicone oil, can be accompanied. Retinal breaks can be sealed with a cryoprobe, diathermy, transcorneal laser or endolaser. Finally, all instruments are removed, and the sclerotomy is sutured if necessary, but with new small instruments self-sealing sclerotomies can be performed.

Pneumatic retinopexy means injection of gas into the vitreous cavity by a needle through the pars plana. Since the gas bubble floats upward, the patient is advised to stay in an appropriate position to ensure that the gas bubble is located excatly at the retinal break. The bubble is believed to push retinal break closed, and then subretinal fluid is absorbed by RPE cells. The area of retinal break is treated with a laser or even with a cryoprobe for creating sufficient scar formation to prevent redetachment.

2.4 Biomaterials

The definition of “biomaterial” according to European Society of Biomaterials Consensus Conference II is "a material intended to interface with biological systems to evaluate, treat, augment, or replace any tissue, organ, or function of the body" (Williams 1999). Biomaterials can be of synthetic or natural origin. Thus, tissues obtained from human or animal tissues, for example bone, cartilage, connective tissue or sclera can also be classified as biomaterials.

The great variety of available synthetic bioabsorbable materials and processing methods makes it possible to create extremely strong implants with long duration of mechanical properties for fixation of fractures and osteotomies (Rokkanen *et al.* 2000). The inclusion of drugs like antibiotics into the material during manufacturing process is also possible (Tiainen *et al.* 2002, Niemelä *et al.* 2006). These kinds of improvements are fascinating and their clinical importance is clear. On the other hand, fast degrading applications can also be made, such as thin films for cell cultures or implants for localised drug delivery (Giordano *et al.* 1997, Yasukawa *et al.* 2001). The rapid development advances continue to widen the research field of bioabsorbable materials and still basic work in developing and producing new bioabsorbable implants for clinical use is actively going on.

2.4.1 Polylactide, polyglycolide and polydioxanone

Polylactide (PLA) is a hydrophobic, semicrystalline polymer belonging to group of poly(α-hydroxyacids). The melting temperature of PLA is 184ºC, while the glass transition temperature is 58ºC (Törmälä et al.1998). PLA is composed of repeating units of lactic acid, which has two stereoisomeric forms, L-and D-isomers. Of these, L-isomer is found in variable levels in human tissues for example as a result of anaerobic glucose metabolism, but the D-isomer is detected only at extremely low levels. The L-isomer has higher mechanical strength and is degraded slower, and thus by increasing the proportion of L-isomer also the mechanical strength increases (Nakamura *et al.* 1989, Törmälä *et al*. 1998). Implants can be made of copolymers containing both L- and D-isomers, also called poly-L,D-lactic acid (or PLDLA or P(L/DL)LA). The proportion of L/D can vary, i.e. 70/30 or 96/4, depending on the application requirements (Törmälä *et al.* 1998).

The amorphosity or crystallinity of the material is related to the microstructural order of molecule chains, which can be totally unordered (amorphous) or the material can be made of parallely ordered molecular chains (crystalline). Due to advantageous properties of L-lactide, pure 100% L-lactide implants were previously developed, but it was discovered that an implant made of poly-L-lactide (PLLA) *in vivo* can be converted into a totally crystallized and brittle form, which was not absorbed in follow-up of over five years (Bergsma *et al.* 1995a, Suuronen *et al.* 1998). These kind of problems have not been reported with PLDLA 96/4 copolymers (Cordewener *et al.* 1995, Peltoniemi *et al.* 1999). Incorporating D-lactide enhances the material degradation, possibly due to the lower crystallinity. Bergsma estimated that histologically the degradation of PLDLA 96/4 at 55 weeks resembled the samples made of PLLA at 143 weeks, evidence of significantly faster degradation (Bergsma *et al.* 1995b).

Polyglycolide (PGA) is another commonly used polymer, which also belongs to the group of poly(α-hydroxyacids). Since it is hydrophilic, it is susceptible to hydrolysis and thus degrades faster than polylactide. Pure PGA implants have been reported to cause sinus formation because of excessively rapid degradation (Böstman *et al.* 1990). However, the initial mechanical strength of PGA is higher than that which can be achieved with similar implants made of PLA. Copolymers of PLA and PGA, called polylactide-glykolide (PLGA), have been widely studied and used especially in pediatric surgery (Ashammakhi & Rokkanen 1995,

Törmälä & Rokkanen 2001). The more rapid degradation can even be beneficial when treating children because of the faster healing processes of damaged tissue.

Polydioxanone (PDS) is a polymer consisting p-dioxanone monomers. PDS is degraded by hydrolysis. The degradation of PDS takes longer than PLA and PGA. PDS has been used as a suture material, for bone fixation and as dural patch (as a copolymer with PLA, commercially available as Ethisorb® Dura Patch).

2.4.2 Bioabsorption

Terms "biodegradable" and "bioabsorbable" are both widely used terms, along with terms "absorbable" and "degradable". Biodegradation refers to a chemical degradation process *in vivo*, whereas degradation refers generally to material breakdown. Bioabsorption is used to refer to breakdown of the material *in vivo*, subsequent metabolism and excretion by tissues or organs.

In vivo bioabsorbable materials undergo gradual degradation process, which can be divided into the phases of hydrolysis and metabolism. The first phase includes chemical cleaving of the molecules of the polymer. The second phase occurs when the cleaved molecules or fragments of material are phagocytosed, mainly by macrophages (Hollinger & Battistone 1986).

The first step of hydrolysis starts with the hydration of the material. The hydration occurs faster in hydrophilic materials (such as PGA) than in hydrophobic materials (such as PLA). It is also faster in the amorphous areas of the material than in crystalline areas. The rate of hydration has a great effect on the degradation speed, because non-specific hydrolysis of ester bonds between lactic monomers occurs by water molecules. Chemical cleaving of the long chains of lactic acid molecules, also called as depolymerisation process, decreases the molecular weight and strength of the polymer, for example depolymerisation of PLGA 70/30 produces monomers in constituent ratio (70% PLA and 30% PGA). Due to this depolymerisation, the mechanical strength of the material decreases even before any macroscopical changes in the implant are detectable so that when major loss of mass starts, there is very little, if any, mechanical strength left (Reed & Gilding 1981, Williams 1982). In the phase of major mass loss, random hydrolysis of molecule chains continues and also fragments of material can be cleaved, increasing the surface area susceptible for hydrolysis.

The second step of the degradation process, metabolism starts when small fragments and molecules of material are phagocytosed, mainly by macrophages and giant cells. In this phase one can detect a reduction in the size of the implant.

After pfagocytosis, the molecules and fragments may undergo further hydrolysis within the lysosomes. Finally, the molecules of the material are metabolized in the citric acid cycle, and the end-products, CO_2 and H_2O, are excreted via respiration (Kulkarni *et al*. 1966). With PGA, also a small amount of glycolic acid is excreted via urine (Hollinger & Battistone 1986).

In vivo, the biodegradation process is enhanced by inflammatory cells, such as macrophages, by the release of free radicals and extracellular enzymes, but nonetheless the main degradation pathway is hydrolysis (Williams 1982, Ali *et al*. 1994). There are many factors which affect the mechanical strength and biodegradation of materials within the body (List I).

I Some factors that can have an effect on strength retention and absorption of polylactide and polyglycolide (Williams 1982, Hollinger & Battistone 1986, Törmälä *et al.* 1998, Kellomäki 2000).

- Chemical composition
- Molecular weight (number of repeat units in polymer)
- Presence of monomers and impurities in material
- Crystallinity
- Molecular orientation
- Processing conditions
- Morphology (presence of stresses within material)
- Surface topography (smoothness)
- Porosity (proportional surface area susceptible for hydrolysis)
- Size and shape (corners etc)
- Site of implantation (vascularity of the tissue)
- Stability of implant fixation
- Sterilization method
- Storage environment

2.4.3 Biocompatibility

When foreign materials are inserted into the body surgically, there is some degree of tissue damage. Host tissue reacts to any material, but the nature and the duration of the response may vary. In the long run, the tissue reactions caused by a foreign material determine the suitability of the material, often called as biocompatibility. The definition of biocompatibility by Williams is “the ability of a material to perform with an appropriate host response in a specific application”

(Williams 1999). The site-specific examination is important because the same material may cause different host responses when placed in different tissues, or when tested in different sizes or shapes. Therefore, any new application should be tested in the location to which the material is planned to be used in its final application.

In 1966 Kulkarni studied PLA as fibers and powder and as a thin film, placed subcutaneously and in abdominal wall in guinea pigs and rats. He detected only a mild inflammatory reaction, with increased fibroblast activity and a collagen fiber layer around implants (Kulkarni *et al.* 1966). Intramuscular reactions were studied later by Cutright and Hunsuck who noted that at first the suture was surrounded by inflammatory cells and foreign body giant cells at 14 days, and the local reaction continued as a chronic reaction with foreign body giant cells throughout the follow-up period of 70 days (Cutright & Hunsuck 1971).

The research on bioabsorbable materials has been very active in the bony environment as a fixation material. Therefore the reactions caused by solid devices made of PLA, PGA and their copolymers in short- and long-term follow-ups are well documented in both experimental and clinical use (Böstman *et al.* 1990, Cordewener *et al.* 1995, Bergsma *et al.* 1995b, Suuronen *et al.* 1998, Peltoniemi *et al.* 1999a, Peltoniemi *et al.* 1999b, van der Elst *et al.* 1999, Rokkanen *et al.* 2000, Ashammakhi *et al.* 2001, Peltoniemi *et al.* 2002, Eppley *et al.* 2004).

The first detectable events in the implantation site are related to the wound and wound healing. There is a formation of a blood clot, swelling of the surrounding tissues due to increased blood circulation and increased capillary permeability. Proteins are adsorbed onto the material surface, becoming denatured or partially denatured. The acute phase includes neutrophilic leucocytes which remove dead cells, bacteria and foreign material particles (Kulkarni *et al.* 1966, Hollinger & Battistone 1986, Tang & Eaton 1995). This acute inflammatory reaction occurs during the first postoperative week.

After the acute phase, with foreign materials in the body, cells in tissues may try to phagocytose the material. If the material cannot be phagocytosed, the cells may try to remove it (for example by extruding it to the skin) or to seal it off from the rest of the body by a connective tissue layer (Tang & Eaton 1995). When using bioabsorbable materials, the tissue reaction continues as a chronic inflammatory reaction until the foreign material has been totally resorbed (Kulkarni *et al.* 1966, Echeverria & Jimenez 1970). The cells responsible for the chronic foreign body inflammatory reaction are mainly mononuclear cells

(macrophages and foreign-body giant cells), fibroblasts and capillaries. Macrophages become activated in the presence of foreign material and they secrete bioactive products, for example various enzymes, prostaglandins, which all may affect the course of the local inflammatory reaction (Williams 1982, Murray & Rushton 1990). Foreign body giant cells (or multinucleated giant cells) are formed by the fusion of macrophages at the site of foreign material. It has been suggested that when new incoming macrophages appear in the site where old macrophages are already present but are incapable of phagocytosing the foreign material, they coalesce to form foreign body giant cells (Mariano & Spector 1974). Macrophages and foreign body giant cells phagocytose particles and monomers that have disintegrated from the material, but they may also attempt to wall-off the material from the rest of the body by forming an encircling cell layer around the implant. In addition, local mild lymphocyte activity and some eosinophils may also appear at the implantation site (Santavirta *et al.* 1990). As the inflammatory reaction continues during the bioabsorption period, connective tissue is produced. When implanted within soft tissues, after all of the foreign material has been resorbed, resolution of the inflammatory reaction occurs leaving only variable amount of fibrous connective tissue (Kulkarni *et al.* 1966, Hollinger & Battistone 1986). In bones, the bioabsorbable materials are entirely replaced by new bone tissue (Vainionpää *et al.* 1986).

2.4.4 Complications with bioabsorbable materials due to tissue reactions

With implants made of some PLA, PGA, PDS or their copolymers, complications have occurred, such as local fluid accumulation leading to fistula formation or osteolysis when placed in bone tissue (Böstman *et al*. 1990, Weiler *et al*. 1996). Rapid degradation may provide material fragments and molecules in high quantities for phagocytosis, exceeding the phagocytosis capacity of macrophages. Local accumulation of lactic monomers lowers the pH, and fluid accumulation increases osmotic pressure. In bone tissues such phenomenon may cause local osteolytic reaction and sterile fluid accumulation (Böstman *et al*. 1990, Törmälä 1992). Tissue reactions to PLA and PGA have been widely studied, and it has been suggested that PGA causes more tissue reactions than PLA (Böstman *et al*. 1990). Also the copolymer of PLA and PGA has been reported to cause more intensive tissue reaction than pure PLA alone (van der Elst *et al*. 1999).

Mechanical strength of amorphous polylactides and polyglycolide materials is weak and degradation occurs in weeks (Vainionpää *et al*. 1989). Self-reinforcement (SR) method was developed by Törmälä *et al*. in Finland (Törmälä *et al*. 1987). It prolonged degradation time from weeks to months and also initial mechanical strength increased, which made it possible to use smaller implants. Self-reinforced material matrix is reinforced by oriented fibers made of the same material as the matrix itself. This can be achieved for example by mechanical die drawing of material in a partially crystalline state, causing deformation of polymer chains into parallel orientation, forming microfibrils into the polymer matrix (Törmälä 1992). Self-reinforcement is lost if the SR-material is heated over glass transition temperature (Tg), when material is melt allowing movement of the molecules from oriented to non-oriented position.

Very slowly degrading PLLA has been reported to have caused swelling at the implantation site in bone three years postoperatively with large implants (Bergsma *et al*. 1995c). The reason for that may be slowly continuing degradation causing particle disintegration from the material and subsequently increasing the surface volume of the PLLA and fibrous tissue causing swelling. Also the high crystallinity of the particles may cause continuous foreign body stimulus to mononuclear cells.

The vascularity of surrounding tissues may have a role in late phases of degradation. It was found out that with SR-PGA pins used for fixation of scaphoid fractures with delayed union there was local fluid accumulation in 25% of patients (Böstman *et al*. 1990). The writers suggested that relatively low vascularity of the scaphoid bone could be the reason for the finding. In cases when screw heads have reached a joint, also aseptic synovial reaction, i.e. intra-articular fluid accumulation has been reported (Barfod & Svendsen 1992).

2.4.5 Tissue reactions to PLDLA 96/4

Tissue reactions, especially to PLDLA 96/4 have been studied both subcutaneously and intramuscularly. Non-reinforced PLDLA 96/4 caused a mild foreign body type reaction in rat subcutis in a follow-up of 1–55 weeks when studied as a solid plate (Cordewener *et al*. 1995). PLDLA 96/4 discs placed subcutaneously caused mild local tissue reactions during a follow-up of 52 weeks (Bergsma *et al*. 1995b). Rods made of SR-PLDLA 96/4 placed intramuscularly in rats caused minimal and well-tolerated reactions with a follow-up period of 6 months (Isotalo *et al*. 1999). SR-PLDLA 96/4 stents (diameter of material 0.2mm)

have been studied in rabbit renal aorta, with a minimal tissue response in a follow-up of 24 months. The stent hydrolysation started after 9–12 months and the material was not visible at 24 months (Hietala *et al*. 2001). In a study by Kangas *et al*. only a thin fibrous capsule had formed during a follow-up of 12 weeks when the PLDLA suture was placed intratendineously (Kangas *et al*. 2006).

In a bony environment, SR-PLDLA96/4 plates (thickness 0.4mm) placed in sheep calvarial bone have been found to cause only a mild tissue reaction, this being highest at the most active bioabsorption period at 1 year. The plate had been absorbed in two years (Peltoniemi *et al.* 1999b). In rabbits, when PLDLA 96/4 sheets were placed over a cranial bone defect this evoked the production of fibrous tissue with macrophages and giant cells with increasing bone formation leading to complete bridging by new bone within 48 weeks (Vesala *et al.* 2002). Intramedullary fixation with SR-PLDLA 96/4 rods in rabbits caused a local very mild foreign body type reaction in a follow-up of 3 weeks to 3 years, and the material had almost totally disappeared after 3 years (Saikku-Bäckström *et al.* 2001). Intramedullar fixation with large SR-PLDLA 96/4 nails (diameter 10mm, length 195mm) evoked a mild reaction in medullar cavity at 6 – 18 months, but by 3 years, the implant had almost totally degraded (Saikku-Bäckström *et al.* 2004). In general, in the previous studies with PLDLA 96/4 as a solid implant, the degradation period was long and tissue reactions towards the material were either minimal or mild during the whole follow-up period.

2.4.6 The effect of fibrous structure on tissue reactions to PLDLA 96/4

Implants made of PLA, PGA or their copolymers have been mainly solid structures, except for suture materials. Improvements in fabrication methods have made it possible to create implants made of multifilament fibres, which can be knitted, woven or braided for creating three dimensional structures. These kinds of implants can have properties that are impossible to achieve in solid structures with PLA, such as slightly compressible or foldable implants.

Theoretically, good strength and long degradation period of a fibrous structure could be achieved by combining large number of mechanically strong fibres. Previously, Kangas *et al.* studied SR-PLDLA sutures *in vitro* (diameter of 0.22mm, draw-ratio of material 6.4), and found that the suture had an initial tensile strength of 424 megapascals (Mpa), with approximately 40% (180 MPa) tensile strength still remaining after 13 weeks (Kangas *et al.* 2001). In a study by

Nuutinen *et al.*, the tensile strength of single SR-PLDLA fibers (diameter 0.27mm, draw ratio 5.0) the initial tensile strength had diminished by 50% after 22 weeks, and almost all (90%) had disappeared after 36 weeks (Nuutinen *et al.* 2003). Knitted stents made of PLDLA 96/4 (fiber diameter 0.27mm, draw ratio 5.0) maintained 50% of compression stiffness for 26 weeks (Nuutinen *et al.* 2002). Even though the fibers were thin, the mechanical strength was retained for a long time period. It must be pointed out that most of the mass degradation occurs after the loss of mechanical strength, therefore the initial tissue healing due to the operation may occur long before the degradation process of the material itself continues to the phases of losing mass integrity and mass metabolism, when most active tissue reaction exists.

The morphology of the implant can affect tissue growth in several ways, for example by guiding tissue growth along the material surface or creating limiting borders for tissue growth.

Implants of fibrous structure have a significantly higher proportional surface area than a solid implant of similar size. The fibrous structure (or porosity) increases the surface area susceptible to hydrolysis which influences the degradation rate and also elevates the surface area available for connective tissue formation and local tissue reactions. The newly formed connective tissue layer around fibrous implant may resemble the shape of the original implant structure (such as a knitted tube). The mechanical tension strength of such implant-connective tissue-hybrid could remain longer than would be expected from the results of *in vitro*–studies of plain implant alone. Due to these reasons it is extremely important to evaluate *in vivo* local tissue reactions for each specific application, mechanical strength and bioabsorption time of fibrous implants.

2.4.7 Experiments with synthetic bioabsorbable materials in ocular and extraocular tissues

Salthouse evaluated tissue reactions to PLGA suture (size 7–0) in rabbit cornea, sclera and ocular muscle, with follow-up periods between 7–60 days (Salthouse *et al*. 1977). He found that the material had been absorbed in 35 days within cornea, 42 days within muscle and 60 days within sclera. Only a minimal or slight reaction was seen in most samples, this being especially minimal within cornea. PDS was evaluated as a suture material for limbal and scleral cataract wound closure (sizes 9–0 and 10–0) (Blaydes & Werblin 1982, Faulborn & Gülececk 1983). The suture material with size 9–0 had disappeared in 90–120 days and

overall performance was excellent (Blaydes & Werblin 1982). However, the corneal sutures with size 10–0 had opened in 13–30 days, and more postoperative irritation was detected when compared with non-absorbables (Faulborn & Gülececk 1983).

PLGA and also PLGA combined with PDS have been studied as implants (mesh or semiflexible membrane) for the treatment of orbital blow-out fractures (Mauriello *et al.* 1993, Hollier *et al.* 2001, Büchel *et al.* 2005). In the study of Mauriello *et al.*, 28 patients were operated using PLGA 910 and followed-up for 1 month to 2 years. Patients did not experience any late complications. Low-grade eyelid inflammation was detected in 4 patients, which all resolved within 4 months (Mauriello *et al.* 1993). Hollier *et al.* used PLGA in 12 patients, with follow-up periods of 0–15 months. It was discovered that the material was acceptable for selected patients (with small bone defects). However, there was one case of an inflammatory reaction leading to implant removal at 7 months (Hollier *et al.* 2001). Buchel *et al.* used semiflexible membrane (thickness of 0.6mm) for the treatment of orbital blow-out fractures and they observed that the material was effective as a supporting implant. There was no clinically detectable inflammatory reaction during the follow-up period of 3–27 months (Büchel *et al.* 2005).

PLGA 910 and PGA have been used as mesh around hydroxyapatite orbital implant after enucleation or evisceration (Jordan *et al.* 1995, Oestereicher *et al.* 1997). The authors reported that none of the patients experienced a foreign body type giant cell reaction to the implant. The motility of prosthesis was improved and the authors recommended the use of bioabsorbable mesh for wrapping the hydroxyapatite implant (Oestereicher *et al.* 1997).

Porous PLGA scaffold has been studied as a round implant (size 8mm x 700mm) for conjunctival reconstruction in an experimental defect. In follow-up periods of 2 and 4 weeks, it was found that PLGA implants modified with collagen and hyaluronic acid caused smaller wound contraction by producing randomly oriented collagen fibers (similar as seen in natural conjunctiva) (Lee *et al.* 2003).

PLGA 910 has also been studied as a mesh made of 5–0 suture fibers for preventing adhesions in reoperations for strabismus (Schmidt *et al.* 1988). In 11 patients previously treated for strabismus and having adhesions in the operated area, the PLGA 910 mesh was used as a barrier between muscle and sclera and/or muscle and Tenon´s capsule for preventing new adhesions. Good results were obtained, and only one patient needed a reoperation due to an over-effect. In one

patient, a histological sample was obtained in the reoperation at 4 weeks postoperatively and many multinuclear cells, some lymphocytes and fibrocytes were seen around material (Schmidt *et al.* 1988).

In 1995 Giordano studied the reaction to PLGA in vitreous space in vitrectomized rabbits (Giordano *et al.* 1995). Microspheres (2.5mg) were injected with basic salt solution into the vitreous cavity and rabbits were followed-up for 2, 4, 8, 12 and 24 weeks. The reactions were evaluated ophthalmoscopically, electroretinographically and histologically. A mild local foreign body reaction was surrounding microspheres after 4 weeks. Retina and choroid seemed normal. Clinically, there was no inflammation after 4 days.

Drug-releasing implants in ocular tissues have been developed, mainly with PLA and PLGA. The material has been loaded with drugs like cyclosporine, 5-fluorouracil, ganciclovir, betamethasone, hrVEGF (human recombinant vascular endothelial growth factor), anti-VEGF aptamer and tacrolimus (Apel *et al.* 1995, Wang *et al.* 1996, Yasukawa *et al.* 2000, Kunou *et al.* 2000, Cleland *et al.* 2001, Yasukawa *et al.* 2001, Sakurai *et al.* 2001, Okabe *et al.* 2003, Carrasquillo *et al.* 2003, Sakurai *et al.* 2003). In these studies, the drug-loaded implants have been used as discs, scleral plugs or microspheres placed subconjuctivally, intracorneally, intrasclerally, transsclerally, or intravitreally.

Bioabsorbable materials can also provide temporary support to which cells can become attached and proliferate, and thus have been studied as substrates for RPE cell cultures. Both PLA and PLGA have been found to be suitable for this purpose, which is also evidence of the good tolerance of the material (Thomson *et al.* 1996, Giordano *et al.* 1997, Lu *et al.* 2001).

2.5 Historical review of materials used for scleral buckling and as cerclage

2.5.1 General tissue reactions and problems with implants

After any operative treatment, local tissue damage and a subsequent healing process starts immediately. The healing process includes not only retinal reattachment and subretinal fluid absorption but also healing of the surgical wound and alleviation of the mechanical stress caused to surrounding tissues by the operation itself and by the implants.

Complications in all methods include persistent detachment of retina and PVR formation. An already attached retina may detach again due to the formation of PVR or new retinal breaks. All surgical procedures include the possibility of infection, cystoid macular edema or formation of epiretinal membranes. There is also a risk of postoperative inflammation. The most feared complication is phthisis bulbi leading to enucleation (American Academy of Ophthalmology 1996).

In scleral buckling surgery, the change in scleral curvature is more extreme when a deeper indentation is achieved, though this is often the desired effect. The operative technique is important since a sufficient indentation needs to be achieved at the correct location with minimum tissue damage. Sutures prevent migration of the implant and the indentation is achieved by correct positioning of the sutures on the sclera along with appropriate tightening. However, if an implant of any material is sutured too tightly, there may be an increase in the ocular pressure, disturbance of ocular blood circulation and even necrosis of ocular tissues (American Academy of Ophthalmology 1996). The method in common use today is to place the implant episclerally on full-thickness sclera. Since the early materials were relatively stiff, the implant was buried intrasclerally in order to secure the position of the implant and to minimize the risk of implant exposure. Some materials, such as gelatin, were found to be too soft and were placed intrasclerally to prevent the cutting of suturing material through the implant. However, comparable results could be achieved with full-thickness scleral implant when compared to intrascleral implant, and therefore the method with minimal morbidity, i.e. an episcleral implant on full-thickness sclera, was claimed to be a better option (Kreissig *et al.* 1992, Gopal *et al.* 2003). It has been found out that the scleral buckling operation, even without an encircling element, can cause a local disturbance in ocular blood circulation (Ito *et al.* 2005, Lincoff *et al.* 2006). A study involving local scleral buckling implant and encircling element, detected a decrease in blood velocity in the choroid and retina in the area of the buckle during a follow-up of 12 weeks (Nagahara *et al.* 2000). The reason for decreased blood circulation may have been compression by the implant, but also tissue damage by cryotherapy could have contributed. The significance of these changes in blood velocity is still unclear, and long term effects are unknown, since changes in blood circulation may become rectified later. Several methods, like cutting the encircling band or suturing with an absorbable suture have been used to avoid the long term effects (Malagola & Pannarale 1994, Schwartz *et al.* 2002, Lincoff *et al.* 2006).

Pain is an important long-term complication, for example in the study of Deokule *et al.* persistent sensation of pain was found to be the second most common reason for implant removal (Deokule *et al.* 2003). Exposure of the implant may be treated by removing the implant, but also conjuctivoplasty or patching the exposed area for example with fascia or cadaver sclera have been studied (Kittredge & Conway 1995). The treatment of any complication related to the implant may require operative removal of buckling implant(s). In order to minimize the risk of erosion or exposure, the development of buckling materials over the years has tended towards softer and more biocompatible implants.

Even with careful operative techniques, there is a possibility of adverse local changes and postoperative complications when using scleral buckling implants or cerclage (List II).

II Local changes and problems related to scleral buckling (Russo & Ruiz 1971, Colosi & Yanoff 1977, McMeel *et al.* 1978, Hahn *et al.* 1979, Deutch *et al.* 1992, Spencer *et al.* 1993, Maguire *et al.* 1993, Saatci *et al.* 1998, D´Hermies *et al.* 1999, Özerturk *et al.* 1999, Farr & Guyton 2000, Nguyen *et al.* 2001, Shami & Abdul-Rahim 2001, Deokule *et al.* 2003, Ünlü *et al.* 2003, Lincoff *et al.* 2006).

- Change of refraction
- Inrease in intraocular pressure
- Scleral thinning or erosion under implant
- Migration of the implant
- Intrusion into vitreous cavity
- Extrusion (or exposure of implant) through conjunctiva and/or eyelid
- Diplopia
- Sensation of foreign body
- Persistent pain
- Infection of foreign material
- Endophthalmitis
- Choroidal detachment
- Local decrease of ocular blood circulation
- Necrosis of ocular tissues
- Anterior segment ischemia

Despite inventions like vitrectomy and pneumatic retinopexy, the scleral buckling procedure is still a commonly used operative method. It has several advantages,

i.e. indentation can be maintained securely by suturing the implant in the desired location. It can be used both episclerally and intrasclerally. The location and the depth of indentation can be checked during the operation. It must be emphasized that without drainage of subretinal fluid, the procedure of scleral buckling (with or without cerclage) can be carried out without perforation of the ocular structures. Thus, the risk of endophthalmitis in such operations is minimal. Furthermore, if necessary, the release of subretinal fluid can be performed and other methods can also be undertaken (American Academy of Ophthalmology 1996, Lincoff & Kreissig 2000).

2.5.2 Nonabsorbable materials

Polyviol

Polyviol (a combination of polyvinyl alcohol and Congo red) was the first material used as a permanent implant for scleral buckling operation by Custodis (Custodis 1953). It was abandoned soon because serious local tissue reactions occurred and the material was considered to be too bulky, needing long intrascleral sutures along the implant (Schepens *et al.* 1960, Lincoff *et al.* 1965).

Polyethylene

A hollow polyethylene was used either as segmental or encircling implant, being placed intrasclerally or with scleral resection (Schepens *et al*. 1957). Polyethylene was relatively stiff and due to round shape of the eye only thin tubes (diameter about 1.0–2.0mm) could be used (Schepens *et al*. 1958, Schepens & Acosta 1991). Therefore, only a minor buckling effect could be achieved. Later, it was noted that the stiffness of polyethylene increased *in vivo* with time leading to local complications (Schepens & Acosta 1991). Histologically, a thin capsule was seen around the material (Dellaporta 1956, Wilson & Green 1987).

Solid silicone and silicone sponge

Solid and spongious silicone implants became available in the 1960´s, and both types are still commercially available (Schepens *et al*. 1960, Lincoff *et al*. 1965). They can be used both intrasclerally and on full-thickness sclera. Solid silicone is

used as a cerclage and as a local buckling element, and a silicone sponge can be used as a local buckling element.

In enucleated eyes, it was found out that a mild local inflammatory reaction surrounded the material but despite this reaction, they were well tolerated (Vogel 1978). In another study, the tissue reaction around silicone sponge buckle consisted of a thin fibrous capsule after 1 month, but also a foreign body granulomatous inflammatory reaction was seen in 5 cases of 13 patients with silicone sponge and in 3 cases with solid silicone (Wilson & Green 1987). In some specimens, proteinaceous fluid and old blood was also present in the implant cavity (Wilson & Green 1987). In human samples with 6 removed implants, calcium deposits were found in the implant surface after long-term follow-up periods. Five of these patients experienced bacterial infections, but one had pain and calcium deposits even without any signs of infection (Brockhurst *et al.* 1993). In a study on patients intented for reoperations, it was found that the capsule around the silicone sponge or solid silicone consisted of dense fibrous layer with a smooth regular surface with the capsule containing a few vessels, some mononuclear cells and occasional fibroadipose tissue (D´Hermies *et al.* 1998). In another study, there was only a capsule layer with no inflammatory cells detected around the silicone implants 18–204 months after implantation (D´Hermies *et al.* 1999a).

With silicone and silicone sponge, all of the above mentioned common long-term complications of permanent implants (i.e. infections, scleral thinning under implant, extrusion through the tissues (conjunctiva and/or eyelid), intrusion to the vitreous cavity, diplopia, persisting pain, increase in ocular pressure, disturbance of ocular blood circulation and necrosis of ocular tissues) are possible. In fact, in studies concerning early and late complications requiring reoperations, most patients have been implanted with solid silicone or silicone sponge materials (Deutch *et al.* 1992, Kreissig *et al.* 1992, Foster & Meyers 2002, Deokule *et al.* 2003).

Hydrogels

Hydrogels are semisolid hydrophilic materials with the ability to absorb water. Three types of hydrogels have been tested, polyglyceryl methacrylate (PGMA), poly(2-hydroxyethyl acrylate) (PHEA), co-poly(methylacrylate-2-hydroxyethyl acrylate) (MAI) but only MAI has been commercially available (Refojo *et al*. 1980, Tolentino *et al*. 1981, Shepens *et al*. 1991). An MAI implant has been used

both episclerally and intrasclerally (Tolentino *et al*. 1981). It was in clinical use for several years but was abandoned due to long-term complications (Shepens *et al*. 1991, Marin *et al*. 1992, Hwang & Lim 1997, Roldán-Pallarés *et al*. 1999). The swelling of hydrogels has been reported to occur to a remarkable degree in a relative volume, i.e. one study reported that the cross-sectional area of hydrogel implants had increased on average by 185% in a group of 28 patients (Oshitari *et al*. 2003). The reasons for implant removal were sensation of foreign body, subconjunctival bulge, ocular motility problems and pain (Oshitari *et al.* 2003, Le Rouic *et al.* 2003). A histological follow-up from 3 weeks to 3 months in rabbits noted that the material was surrounded by a capsule of connective tissue. In three weeks there was a mild inflammatory reaction but in 3 months there were almost no inflammatory cells (Refojo *et al.* 1980). Later in experimental studies in rabbits with a longer follow-up it was found that the material became surrounded by a capsule of connective tissue, but the inner surface of the capsule contained deposits of material (indicating material fragmentation) surrounded by foreign body giant cells (D´Hermies *et al.* 1995, D´Hermies *et al.* 1999b). Findings of irregular inner surface of capsule and foreign body giant cell granulomas have also been found in human samples (D´Hermies *et al.* 1998, D´Hermies *et al.* 1999a).

e-PTFE and silicone band coated with e-PTFE

Expanded polytetrafluoroethylene (e-PTFE, also know as Gore-Tex™) has been studied with various pore sizes (Lobes *et al.* 1981, Tawakol *et al.* 1989, Korobelnik *et al.* 1999, Korobelnik *et al.* 2000, Sheu *et al.* 2001). In an evaluation of enrolled thin layer of porous e-PTFE, it was found out that there was colonisation of material with fibrocellular tissues and adhesions to surrounding conjunctival tissue (Lobes *et al.* 1981, Tawakol *et al.* 1989, Korobelnik *et al.* 1999, Sheu *et al.* 2001). This kind of colonisation by fibrovascular tissue may be good for preventing migration or exposure, but may also represent an extra challenge if removal is required. In these studies, the tissue reaction was rated to be minimal or only a mild inflammatory reaction. The material was described in most studies as being well tolerated or to display good biocompatibility, except for the study of Sheu *et al.*, who discovered massive adhesions (Lobes *et al.* 1981, Tawakol *et al.* 1989, Korobelnik *et al.* 1999, Sheu *et al.* 2001).

Three weeks after insertion of an implant made of a silicone band, coated with e-PTFE (S/e-PTFE), massive adhesions from material to the surrounding

tissues had developed, accompanied by a local inflammatory reaction. There was also colonisation of the material by inflammatory cells, and granulomas with calcium deposits were observed (Mortemousque *et al.* 2001, Mortemousque *et al.* 2002).

In the clinical study by Roldan-Pallarés and Awad-el Susi, an implant made of PTFEe was used in 32 patients with RRD, with the average follow-up period being 11 months (Roldan-Pallarés & Awad-el Susi 2000). There were no complications and the writers reported excellent tolerance with good biocompatibility to the material throughout the whole follow-up period.

Other nonabsorbable materials

Although the first synthetic material was a cotton swab, tissue reactions to that material were not studied (Jess 1937).

Braided nylon suture 2–0 (Supramid®) and polyester (polyethylene terephthalate, commercially available as Mersilene®) have been used as encircling elements (Kommerell 1972, Kommerell & Dünzen 1977, Witschel & Faulborn 1978). A moderate granulomatous inflammatory reaction was observed around the nylon suture material, but it was considered not to be clinically significant because of the amount of the material. However, a thin single suture may cause erosion of underlying sclera leading to intrusion of the material, also called a string-syndrome (Witschel & Faulborn 1978). Mersilene® has also been studied as 5 mm broad band and it seemed to be generally well tolerated by tissues (Witschel & Faulborn 1978). In one case, there was erosion under the band, leading to intrusion through sclera to the choroids.

Polyglycol methacrylate was also tested episclerally and the material was claimed to be suitable for scleral buckling (Kristek *et al.* 1966). An episclerally placed silver clasp has been tested but it was advised that it would be best to remove it in a subsequent operation 6 months later (Gloor *et al.* 1977).

2.5.3 Absorbable materials

Absorbable materials can be of biological or synthetic origin. They can be derived from animal or human tissues (donor or autologous). Several biological (nonsynthetic) materials have been used, such as catgut, chromic catgut, tendon, tarsus, sclera (donor), fat, stabilized human or bovine fibrin, fibrin sponge, fascia, dura mater or skin. There are problems with biological materials e.g. availability,

the possibility of viral infections and immunological problems (with donor tissues) and donor site morbidity (with autologous tissues). There may also be variability within the material. Materials of biological origin are bioabsorbable in tissues, but their bioabsorption rate may vary greatly. It may also be difficult to mold biological material into an implant of the desired shape and size.

Gelatin and collagen

Gelatin is prepared by partial hydrolysis of collagen from animal tissues such as skin and bones. Gelatin has been used in films or sheets with thickness of 0.5mm or 0.75mm. It was placed intrasclerally due to the possibility of cutting through the material when tightening sutures (Wilson 1983). Gelatin must also be hydrated before implantation, even for as long as 40 minutes, which may increase valuable operation time. The material could be rolled to the desired buckle thickness or placed in layers, and could be used under cerclage. The material created a buckle which remained for 1–2 months, then disappeared during the next few months (Borrás 1961, Jacklin *et al.* 1968, Daniele *et al.* 1968, King *et al.* 1975, Levit *et al.* 1975, Tanenbaum & Chandra 1976, Freilich & Morton 1981, Wilson 1983). An inflammatory reaction with giant cells was seen in the microscope. The reaction was defined as slight or medium, and it was localised and well defined and no damage to sclera, choroid or retina was seen. The material was found to be suitable for scleral buckling (Borrás 1961, Daniele *et al.* 1968). In reoperations, it was found that after 8 weeks the implant had softened and fragmentation had started (Jacklin *et al.* 1968). Donor tissues such as sclera could be used episclerally when rolled, creating an indentation lasting for a few months which then became flatter during the next few months. The tissue reaction was a localised inflammatory reaction, without toxicity or tissue necrosis and the implant was described as being well tolerated.

Catgut and chromic catgut

In a series of experimental works by Dellaporta, surgical catgut and chromic surgical catgut were used as 4–0 suture material for creating a temporary indentation (Dellaporta 1956, Dellaporta 1962a, Dellaporta 1962b, Dellaporta 1962c and Dellaporta 1966). One or two sutures were placed as encircling elements within scleral folds or intrasclerally in experiments conducted in dogs. A considerable inflammatory reaction was reported to occur in the choroid and

ciliary body within the operation site, lasting for 10 days (Dellaporta 1962a, Dellaporta 1962b, Dellaporta 1962c and Dellaporta 1966). One possible reason for this could be the extensive operative technique, since securing mattress sutures (surgical chromic gut or silk) were placed all the way along the encircling scleral folds or there were intrasclerally placed chromic gut sutures. The indentation effect lasted from 5 weeks to 2 months with chromic catgut and then became flattened. The plain surgical catgut caused an indentation which lasted for about 1 week and then flattened, and the material was absorbed within a few weeks. There were leukocytes and lymphocytes seen around material. The chromic surgical gut was surrounded by inflammatory cells, lymphocytes and fibroblasts before total degradation in about 5 months (Dellaporta 1962a and Dellaporta 1962c). At 13 months postoperatively, the sclera was found to be normal (Dellaporta 1966).

Fibrin

Fibrin was used as a rod (diamaters of 0.6, 0.8 or 1.1mm) or fibrin sponge, being placed intrasclerally in humans. The indentation lasted for only a few weeks, but good clinical results and no complications attributable to the material were reported (Grósz *et al.* 1976, Wollensak & Engels 1977). One sample (12 days postoperatively) was analysed histologically and there was a diffuse infiltration of cells within resected sclera, with round cells, monocytes and a few foreign body giant cells. Moderate infiltration of choroid was also seen, but the retinal structure was normal, although detached in some areas (Grósz *et al.* 1976).

Other tissue transplants and injectable absorbable materials

Other tissue transplants have been widely studied. Tendon autograft provided indentation for 3–4 months with good tissue tolerance (Scott 1964). In addition, autologous fascia transplants from temporalis muscle and fascia lata, evoked minimal histologic reactions, no foreign body giant cells or inflammatory reaction (Chilaris *et al.* 1973, Minning & Havener 1983). These autologous materials had, however, the possibility of donor site morbidity. Autologous tarsus from the operated eye was also used in a scleral pocket, causing an indentation lasting for 2–8 weeks, with results being described as good (Mortada 1969).

Donor collagen prepared from cattle tendons were used as sheets, placed intrasclerally. The indentation effect maintained unchanged for 6–8 weeks, then

started to flatten, which continued for over 10 months. It was reported that the material had become a part of surrounding tissues (L´Esperance 1966). Rolled sclera has been used episclerally creating an indentation lasting for a few months subsequently flattening during the next few months. The tissue reaction was a localised inflammatory reaction without tissue necrosis and the material was described to be well tolerated (Cibis & Knobloch 1967, Francois *et al.* 1979). Lyophilized sclera with histoacryl tissue adhesive has also been tested evoking only a localised inflammatory reaction, with good clinical results (Vygantas & Kanter 1974, Regenbogen *et al.* 1976). Dura mater was used in 76 patients, and no complications due to the material were reported (Winter & Khorram-Sefat 1988). Also skin has been used as an episcleral and intrascleral implant with good clinical results, local reactions were slight and well tolerated in most cases (Chien 1978, Zeng *et al.* 1992). There were a few patients who experienced severe local reactions, all in patients operated also by shortening of the sclera (Chien 1978).

The tissue reaction to subscleral injection of air was not described (Smith 1952). The homogenized autologous fat was resorbed slowly but incompletely from the subscleral space though no histological samples were taken (Sachsenweger & Hartwig 1975). Sodium hyaluronate has also been injected into subscleral space creating a temporary effect (Poole & Sudarsky 1986, Mittl & Tiwari 1987). Material was seen for 7–14 days. Histological display showed no inflammatory cells but there was evidence of a few intrachoroidal cysts and fibrosis in the choroid (Mittl & Tiwari 1987).

Polyurethane foam

Polyurethane foam has been studied experimentally in rabbits and clinically in patients (Kothe *et al.* 1985, Kothe & Lommatzsch 1985). In a follow-up ranging from 2 weeks to 72 weeks, there was evidence of fibrocyte growth, foreign body type reaction and granulation tissue throughout the implant after 24 weeks and the structure of the implant was visible after 48 weeks. The material was considered to have been incorporated rather than bioabsorbed by surrounding tissues, although polyurethane foam is slowly bioabsorbable (Törmälä *et al.* 1998). The results were considered to be good, in 165 patients the material was well tolerated with few complications (Kothe & Lommatzsch 1985). The material was described as being less elastic than silicone sponge.

Urethane-based polymer used as a suprachoroidal material evoked an acute inflammatory reaction after a few hours, and foamy macrophages were seen at the

implantation site around the material at 2, 8 and 10 months. At 13 months, the material had disappeared, but local scleral thinning and macrophages were present and there was local fibrosis in the choroid (Foulds *et al.* 1988).

PLA, PLGA and PDS

Wilson used synthetic absorbable materials, PG910, PGA and PDS as encircling elements in rabbits (Wilson 1983). The material was made of braided fibers. The encircling indentation effect lasted for 1 month with PG910 and PGA, and 10 weeks with PDS in rabbits. PG910 was also used in 20 patients as an encircling band, with or without a segmental gelatin buckling element. At 4 weeks, in 12 patients (of 20) there was little or no indentation left when examined with indirect ophthalmoscopy, and in all cases the encircling indentation had flattened by 8 weeks. Clinically, no abnormal reactions were seen. Histologically, in rabbits a minimal foreign body reaction with foreign body giant cells and fibroblasts was detected with PGA 910 and PGA, and degradation continued up to 6 months. PDS was surrounded by a minimal tissue reaction with foreign body giant cells (Wilson 1983).

Marti *et al.* used commercially available absorbable synthetic sutures as a rolled net made of polyfilaments of PGA and PG910 and monofilaments of PDS. Also PDS clips were used. In surgical experiments in rabbits, PG910 was absorbed by the second month, and 90% of the PGA by the third month. In humans, PDS absorption began after the fourth month and the indentation reduced by 0.5–0.8mm/month (Marti *et al.* 1986, Marti *et al.* 1987, Marti *et al.* 1988). In the histological evaluation, a mild chronic inflammatory reaction was seen around the implantation site. No complications were found due to material and in general the implants were described as being well tolerated with PGA 910, PGA and PDS (Marti *et al.* 1986, Marti *et al.* 1987, Marti *et al.* 1988).

In the early 1990`s, Guthoff *et al.* used an implant made of PG910 (7 parts) and PDS (1 part) in a cylindrical form. In rabbits, the implant created a buckle that decreased rapidly, from its original size (3.2–4.0mm) down to 2.0mm in two weeks and to 0.5mm in 5 weeks (Guthoff *et al.* 1993). Histologically, a slight resorptive reaction with inflammatory cells was found at the implantation site, but there was no scleral thinning or infiltration by inflammatory cells. The results were considered to be good (Guthoff *et al.* 1993).

Biardzka and Kaluzny used PDS size 0 as single encircling suture episclerally in rabbits and patients (Biardzka & Kaluzny 1988). It was found out that the

indentation started to flatten after 3 months and had disappeared by 5 months. In the histological evaluation it was observed that the material was unchanged for 4 months, but had disappeared by 6 months. The local tissue reaction around the implant consisted of mononuclear cells and some foreign body giant cells at 3 months, whereas by 6 months, the suture had been replaced by connective tissue. The material was considered to be well tolerated with no complications attributable to the material (Biardzka & Kaluzny 1988).

3 Purpose of the present study

Bioabsorbable materials have been used in a variety of clinical applications in patients for years with good results. Bioabsorbable implants made of fibrous structures have several properties which may affect the degradation time and local tissue reactions. This experimental study in rats and rabbits was performed to investigate the suitability of fibrous bioabsorbable PLDLA 96/4 implant for use in scleral buckling in retinal detachment surgery.

The specific questions asked in this study were:

1. What is the behaviour of fibrous implant made of self-reinforced PLDLA 96/4 in soft tissues in rats during the first 48 weeks after insertion? (I, II)
2. Can bioabsorbable episcleral implant provide sufficient indentation of sclera in rabbits at 1, 3 and 5 months? (III)
3. What are the local tissue reactions of fibrous implants made of self-reinforced PLDLA 96/4 when placed episclerally in rabbits during the first 48 weeks after insertion? (III, IV)
4. Are the duration of indentation effect and biocompatibility of fibrous implant made of PLDLA 96/4 suitable for clinical use for scleral buckling in retinal detachment surgery based on experimental studies in rabbits having a follow-up of 48 weeks? (III, IV)

4 Materials and methods

4.1 Implants

All bioabsorbable implants used in these experimental studies (I, II, III, IV) were manufactured in the Institute of Biomaterials, Tampere University of Technology, Tampere, Finland. The implants were made of poly-L/DL-lactide 96/4 (molar ratio of L/DL). The raw material was PLDLA 96/4 (PURAC Biochem B.V., Corinchem, Holland). The manufacturing process of filaments consisted of an extrusion, which was followed immediately by a drawing process and in this way a self-reinforced structure was created.

Study I: Implants were made of woven tubular knitting that was made by 8 fibers, each of them made of 4 filaments. The original diameter of the filaments was 120µm. The fabrication method included rolling of knitted tube into a cylinder with a diameter of 15mm and thickness of 3.5mm (Figure 1) (Honkanen *et al.* 2003). The implants were made loose, ordinary and dense disc-shaped implants weighing 200, 250 and 300mg, respectively. Implants were washed and dried with ethanol, packed as commercial bioabsorbable devices and sterilized by gamma irradiation (minimum dose of 2.5 MRad). The fibrous disc-shaped PLDLA implants of three densities were macroscopically similar in size and shape.

Study II: Implants were made of eight-ply multifilament yarn, with 100µm diameter in each filament. The multifilament yarns were knitted to tubular mesh using a tubular single jersey knitting machine (Textilmachinenfabrik Harry Lucas GmbH, Neumünster, Germany). Each implant was 5cm long, 1cm broad and 2mm thick (Figure 2). The implants were cleaned and dried with ethanol, packed as commercially available bioabsorbable devices, and eventually sterilized by gamma irradiation (minimun dose of 2.5 MRad). Knitted tubular PLDLA mesh was very easily foldable. It was not streching and the surface of the knitted structure was even.

Studies III and IV: Bioabsorbable and silicone sponge implants were used. The bioabsorbable implants were made of melt-spun eight-ply multifilament with an individual filament diameter being 100µm (Gimac microextruder, Castronno, Italy). The multifilament was knitted into a tubular single jersey knitting machine (Elha R-1S, Textilmaschinenfabrik Harry Lucas GmbH, Neumünster, Germany) using 9 needles. Thermally treated tubular knitting was stuffed with textured

PLDLA 96/4 filaments and the ends of the tubes were closed by heat-sealing. Since filling was done manually, the implants were macroscopically slightly variable in their diameter and therefore the original implant diameters ranged from 3.0mm to 3.5mm. The knitted surface of the implant was even and did not feel rough to touch. The implants were originally 30mm long (Figure 3A). In the operating room, they were cut with a hot wire loop into 10mm-long implants. All bioabsorbable implants were sterilized by gamma irradiation (minimum dose of 25 kGy). A Mira no. 504 round silicone sponge (Mira Inc., Waltham, MA, USA) was used as control material, with an implant length of 10mm, and a diameter of 4mm (Figure 3B).

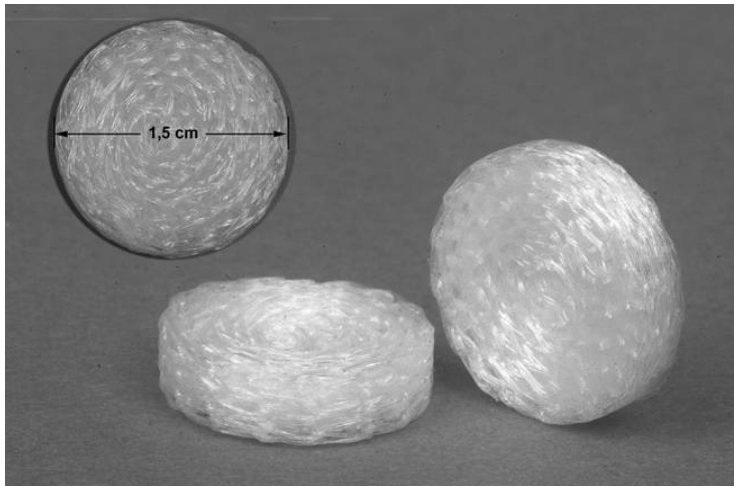

Fig. 1. Disc-shaped bioabsorbable knitted implant, diameter 15mm, thickness 3.5mm.

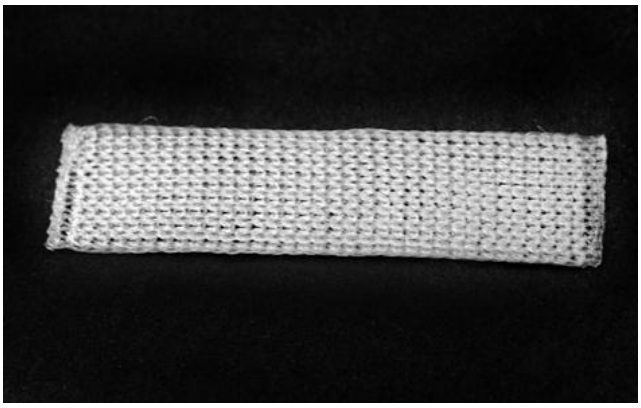

Fig. 2. Tubular knitted mesh made of bioabsorbable PLDLA 96/4 fibers, length 5cm, breadth 1cm, and thickness 2mm.

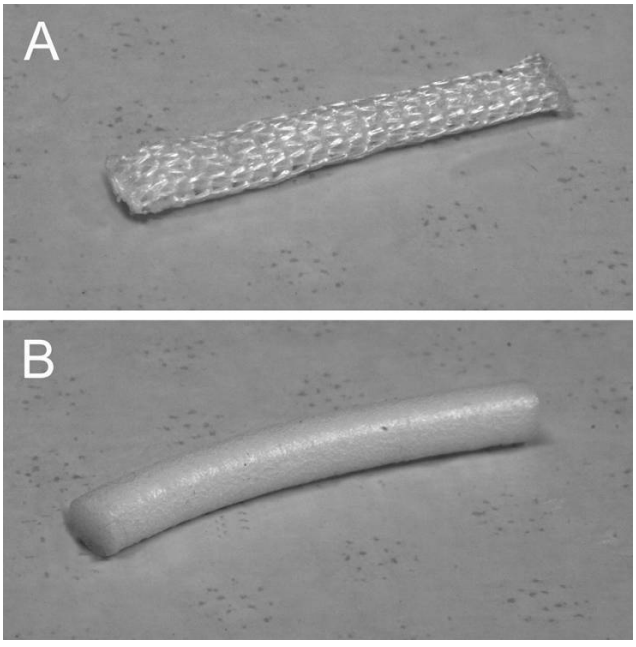

Fig. 3. A) A tubular PLDLA scleral buckling implant made of PLDLA 96/4 fibers, length 3cm and diameter 3 – 3.5mm. B) A silicone sponge implant, length 3cm and diameter 4mm (Mira no. 504, Mira Inc., Waltham, MA, USA).

4.2 Experimental animals and models

These works were approved by the Animal Research Committee of the University of Oulu, and by the Provincial Administrative Board, according to Finnish law. The guidelines of the ethical committee of the Oulu University Experimental Animal Center for the care and use of experimental animals have been observed.

Study I: Thirty-two Sprague-Dawley male rats of 16–19 weeks old (mean 17weeks), weighing 330–460g (mean 405g). Follow-up periods were 3 days, 1, 2, 3, 6, 12, 24 and 48 weeks.

Study II: Thirty-five Sprague-Dawley male rats weighing on average 417g (range 355–445g) were used with follow-up periods of 3, 6, 12, 18, 24, 36 and 48 weeks, with five rats in each follow-up group.

Studies III and IV: Forty-eight New-Zealand White male rabbits weighting 2600–2800g, received implants with follow-up periods of 1 month (six rabbits), 3 months (six rabbits), 5 months (30 rabbits) and 12 months (six rabbits).

4.3 Surgical procedures and anaesthesia

4.3.1 Subcutaneous implants

Study I: The rats were anaesthetized with intraperitoneal injection (3.3ml/kg) of a 1:1 mixture containing fentanyl-fluanisone (Hypnorm®, Janssen Pharmaceutical, Inc, Beerse, Belgium) diluted in water 1:1, and midazolam (Dormicum® 5mg/ml, Roche Oy, Espoo, Finland) diluted in water 1:1.

The site in incision was shaved and then sterilized with chlorhexidine. Four PLDLA disc-shaped implants were implanted in pockets that were dissected in the dorsal subcutaneous tissue of each of the 32 rats. The implants were fixed in place using two non-absorbable, polyamide stitches (4-0 Dermalon®, Sherwood Medical, St. Louis, MO, USA). The skin was then closed using non-absorbable similar polyamide sutures. Analgesia was provided postoperatively by using s.c. 0.1–0.5ml/kg injections of buprenorphine (Temgesic®, Reckitt & Colman Pharmaceuticals, Inc, Richmond, England) administered immediately after the operations. Rats were given regular pelleted rat food and tap water *ad libitum*. They were kept in cages in groups of 4–6 rats in an artificially illuminated room, with 12 h of light and 12 h darkness. The rats were sacrificed by using carbon dioxide.

Study II: The rats were anaesthetized with an intraperitoneal injection (3.3 ml/kg) of a mixture containing fentanyl-fluanisone (Hypnorm®, Janssen Pharmaceutica, Inc, Beerse, Belgium), Saundertone, U.K.), diluted in water 1:1, and midazolam (Dormicum® 5mg/ml, Roche Oy, Espoo, Finland) also diluted in water 1:1. The site of the incision was shaved and then sterilized with chlorhexidine. A 4cm incision was made in the midsection of the back. Two implants, one on each side, were placed into the subcutaneous pockets that were dissected in the subcutaneous tissue. The implants were sutured with a 4–0 nonabsorbable (Dermalon®, Sherwood Medical, St Luis, MO, USA) suture on the cranial end of the implant, and with absorbable 4–0 suture (Vicryl®, Ethicon, Inc., Somerville, NJ) on the caudal end of the implant in order to prevent growth disturbance, but intented to prevent implant movement. Skin was closed with absorbable 4–0 sutures (Vicryl®, Ethicon, Inc., Somerville, NJ). Analgetics were provided postoperatively to all rats with s.c. 0.1–0.5ml/kg injections of buprenorphine (Temgesic®, Reckitt & Colman Pharmacceuticals, Inc, Richmond, England) at the end of operation. Rats were given pelleted rat food and tap water *ad libitum*, and they were kept in cages in groups (4–6 rats in each cage) in an artificially illuminated room, with 12h of light and 12h darkness. At the end of the follow-up period the rats were killed with carbon dioxide.

4.3.2 Episcleral implants

Studies III and IV: The rabbits were anaesthetized with an intramuscular injection consisting of ketamine hydrochloride (Ketalar®, Parke-Davis, Warner Lambert Nordic, Solna, Sweden) (50mg/ml), 20mg/kg and medetomine hydrochloride (Domitor®, Orion Oyj, Espoo, Finland) (1mg/ml), 0.3mg/kg. Cefuroxime (Zinacef®, Glaxo Operations UK, County Durham, UK), 250mg, was given subcutaneously at the beginning of the operation as infection prophylaxis.

Operations were carried out on the left eye of each rabbit. The conjunctiva was opened from the limbus on the superior temporal quadrant (Fig. 4A). The implants were placed 7 mm posterior to the limbus. The implants were sutured episclerally with two 5-0 polyester U-shaped sutures (Mersilene, Ethicon, Johnson & Johnson, Brussels, Belgium) on both ends of each implant (Fig. 4B). The sutures were fastened to moderate tightness. All implants were placed circumferentially on the superior temporal quadrant just temporal to the superior rectus muscle. Finally, the conjunctiva was sutured with 8-0 silk (Virgin Silk, Ethicon, Johnson & Johnson, St-Stevens-Woluwe, Belgium) (Fig. 4C).

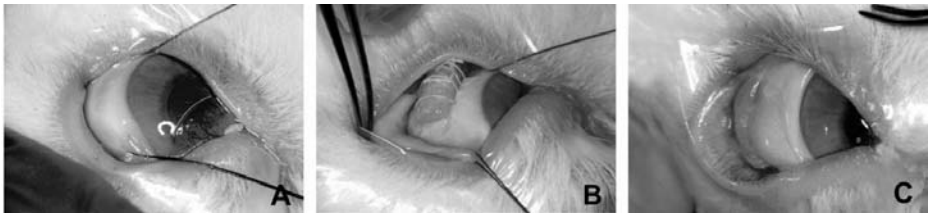

Fig. 4. A) All implants were placed on the superior temporal quadrant of the left eye. B) PLDLA 96/4 implant episclerally, sutured with two U-shaped 5-0 Mersilene sutures. C) PLDLA 96/4 implant in place under the conjunctiva.

Postoperatively all animals were subcutaneously given buprenorphine (Temgesic®, Schering-Plough Europe, Brussels, Belgium) (0.3mg/ml), 0.15mg twice a day for three days. Timolol maleate (Blocanol depot®, 5mg/ml, Merck Sharp & Dohme B.V., Haarlem, Holland) 0.5% eye-drops were administered once a day for three days and a combination of dexamethasone, 0.1%, and chloramphenicol (Oftan Dexa-Chlora®, Santen Oy, Tampere, Finland) eye-drops were given twice a day for two weeks to all rabbits. Prior to CT scanning, the rabbits were sedated with an intramuscular injection (0.3–0.5ml) of a combination of fentanyl citrate (0.315mg/ml) and fluanisone (10mg/ml) (Hypnorm®, Janssen Pharmaceutica, Beerse, Belgium). Before enucleation, the rabbits were sedated with an intramuscular fentanyl citrate and fluanisone (0.5ml), then given an overdose of pentobarbital intravenously (Mebunat®, Orion Oyj, Espoo, Finland).

4.4 Specimen processing

Study I: For harvesting the samples, the skin was opened from the area of the scar, and the sites of implants were gently revealed. The implants were removed with 5 mm of surrounding tissues and they were fixed with 10% formalin in phosphate buffered saline (PBS) for 3–5 days. The histological samples were routinely processed and embedded in paraffin. The block was cut from the middle of the implant and several 5µm sections were cut from each sample and they were stained with haematoxylin-eosin (HE) and van Gieson.

Study II: Skin was opened for harvesting the samples and the implant sites were gently revealed. One implant was removed with a minimal amount of surrounding tissues and it was tested mechanically for tensile strength. The other one was removed with surrounding tissues and it was fixated with 10% PBS formalin for five days, then they were routinely processed and mounted in

paraffin. Several 5µm sections were cut from each sample from the middle and also from each end of the implant. Sections were stained with HE and van Gieson.

Studies III and IV: At the end of each follow-up period, the animals were sacrificed and both eyes enucleated. The specimens were fixed in 10% phosphate-buffered formalin for 3 days. The samples were routinely processed and mounted in paraffin. The blocks were cut precisely perpendicularly to the longitudinal axis of the implant. Several 5µm sections were cut from each sample from the middle of the implant and stained with HE and van Gieson stain.

4.5 Methods of analysis

4.5.1 Clinical and macroscopical observations

The animals were checked every day for the first two weeks and then weekly for any abnormalities. During harvesting, the implant sites were studied for macroscopic changes.

4.5.2 Light microscopy

Studies I and II: General examinations of HE and van Gieson -stained sections were performed under light microscopy and with polarized light. Special attention was paid to the in-growth of fibro-inflammatory tissue and defining cell types.

Study IV: HE and van Gieson-stained sections were analyzed. The retina, choroid, and cornea were evaluated for any microscopic changes. The contralateral non-operated eye of each rabbit was also examined. The implant material was evaluated under polarized light for the appearance of individual fibers at each follow-up period.

4.5.3 Histomorphometrical analysis

Measurement of the PLDLA filament diameters was done by MCID M4 digital image analysis system, with software version 3.0, rev 1.1 (Imaging Research, Inc., Brook University, St. Catharines, Canada).

Study I: PLDLA 96/4 fiber diameter was measured from three samples of each implant type (dense, ordinary and loose) at 2 week, 24 weeks and 48 weeks.

In each specimen, the diameter of a minimum of 10 fibers was examined from at least 4 randomly selected areas in each slide.

Study II: Fiber diameter was measured from at least 3 separate samples, from 10 view areas, containing a minimum of 30 values, at 2 weeks, 24 weeks and 48 weeks.

Study IV: The diameter of the PLDLA 96/4 fiber was measured at all follow-up times; three implants at 1, 3 and 5 months, and 2 at 12 months. In each specimen, the diameters of 8–21 fibers were examined from at least 3 or 4 randomly selected areas in each microscopic slide.

4.5.4 Radiological analysis of indentation depth

Study III: All rabbits underwent CT scanning under sedation at one week, and three and five months postoperatively. Helical computed tomography (CT HiSpeed Advantage; GE, Milwaukee, WI) was used in a transaxial direction by turning the head of the rabbit to the left so that the X-ray beam was as perpendicular to the implant as possible. The parameters were 512 x 512 matrix, 80kV and 50mA, 3mm collimation with 2mm section overlap, so that 10 slices from each eye at the point of the implants were obtained. All imaging data was transferred to a computer workstation (Advantage Windows 2.0 using a Sun Sparc 20; GE Buc) for measurement.

Of the 10 images produced, we chose for measurement the one in which the diameter was closest to the 3–4mm real thickness of the implant and the depression on the bulbus surface was deepest. A manually controlled circle was placed on the outer surface of the bulbus so that the circle and the outer surface of the bulbus next to the implant were at the same level. The distance between the circle corresponding to the outer surface of the bulbus and the deepest indentation point on the inner surface of the bulbus was measured (Figs. 5A and 5B). This distance was measured to the nearest 0.1mm. The diameter of the bulbus was measured from the image in which the lens was biggest. The diameter was measured parallel to the posterior surface of the lens (Fig. 6).

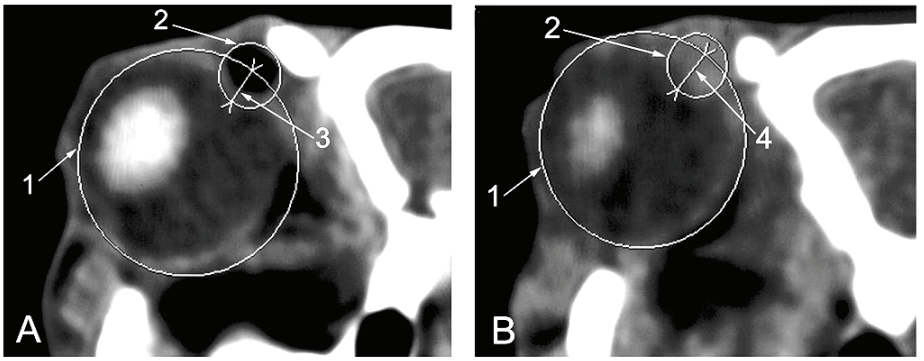

Fig. 5. Measurements of indentation with a silicone sponge implant (A) and with a PLDLA 96/4 implant (B). The silicone sponge implant is seen as a dark round area (A). The PLDLA 96/4 implant causes scleral indentation (B), but the implant itself is not distinguished from the sclera, since both PLDLA 96/4 and sclera have the same density in CT. 1 = A first manually controlled circle placed on the outer surface of the bulbus. 2 = A second manually controlled circle placed on the point of the deepest scleral indentation caused by the implant. 3 & 4 = The distance between the outer surface of the bulbus and the deepest indentation point on the inner surface of the bulbus; 3 = with a silicone sponge implant, and 4 = with a PLDLA 96/4 implant.

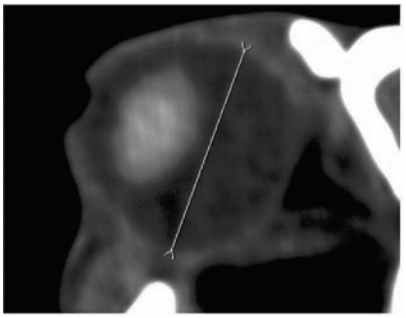

Fig. 6. The diameter of the bulbus was measured at its largest point, parallel to the posterior surface of the lens.

4.5.5 FESEM analysis of the knitted tubular mesh implants

Study II: Field emission scanning electron microscopy (FESEM) was performed with FESEM, JEOL JSM-6300F (JEOL LTD, Tokyo, Japan) at an accelerating voltage of 6kV. In the FESEM studies, one implant segment (from the paraffin blocks) from each follow-up period was deparaffinised in xylene and rehydrated

in an ethanol series. For coating, the specimens were first dehydrated in ethanol series and then subjected to critical-point drying with carbon dioxide in a critical point dryer (BAL-TEC CPD 030, BAL-TEC Ltd., Balzers, Liechtenstein). Then, implant specimens were mounted on metal stubs using conductive carbon cement and finally coated with platinum-palladium (Agar Scientific Ltd., Stansted, UK).

4.5.6 Evaluation of the amount of connective tissue

Study I: From samples of 48 weeks follow-up (n = 15), the percentage of area occupied by dense connective tissue and loose connective tissue were measured using the point counting method as used by Pääkkö *et al.* (Pääkkö *et al.* 1989). For measurements, a Leitz Dialux microscope with a net micrometer of 100 points in one eyepiece was used. The magnification for counting was x400. Counting was done on 10 randomly chosen consecutive view areas. The total number of counted points for estimating the parameters was 13000.

4.5.7 Statistical methods

Studies I, II and IV: Means and standard deviations (SDs) of measurements of fiber thickness were calculated.

Study I: Dense connective tissue measurement means and standard deviations (SDs) were calculated. Analysis of variance (ANOVA) was used and when differences were found Student's t-test was used to evaluate which groups differed. The results were analyzed using SPSS 12.0 software (SPSS Inc., Chicago, Ill., USA). Two-tailed p values were reported.

Study III: Indentation depth measurement means and SDs were calculated and Student's t test was used to compare results between the groups. ANOVA for repeated measurements was utilized for comparison of indentation. The results were analyzed using SPSS 10.0 software (SPSS Inc., Chicago, Ill., USA). Two-tailed p values were reported.

5 Results

5.1 Macroscopic results

Studies I and II: The postoperative period was uneventful in all rats. No infections or complications occured during the study and all rats reached the planned follow-up period. At the end of longest follow-up of 48 weeks, both implant types, disc-shaped and tubular implant filled with PLDLA96/4 filaments, were clearly visible and macroscopically they had maintained the original shape and size. After 48 weeks of follow-up, the PLDLA 96/4 fibers were macroscopically visible. They were tightly attached to surrounding tissues.

Studies III and IV: Operations with PLDLA implants were possible to perform with a similar technique as that used with a silicone sponge. Handling of the material was slightly different since PLDLA is not as compressible as a silicone sponge and therefore the tightening of the U-sutures was not as easy as with the silicone sponge. Despite differencies in handling properties of PLDLA implant, they were possible to manage.

Postoperative recovery was uneventful in all rabbits. There was only mild conjunctival hyperemia for a few weeks postoperatively in both experimental groups. Three rabbits died during CT scanning at 3 months postoperatively due to anaesthesia complications (2 in the silicone sponge group and one in the PLDLA group). One more rabbit (silicone group) had to be sacrificed at 17 weeks because of refusal to eat. An autopsy was conducted on all the four rabbits, but there were no macroscopic or microscopic signs of any ocular or other problems. Even at 48 weeks postoperatively, the bioabsorbable implant was clearly detectable, showing no macroscopic biodegradation and the PLDLA 96/4 fibers were macroscopically visible. The implants were tightly attached to sclera by sutures.

5.2 Change in thickness of PLDLA 96/4 filaments

The diameters of individual filaments remained within the limits of variation both subcutaneously in rats and episclerally in rabbits (Table 1). At 48 weeks, most filaments contained cracks which made measurements more difficult and inconclusive.

Table 1. Diameter of PLDLA 96/4 filaments after follow-up periods from 2 to 48 weeks.

Study	Follow-up			Significance
	2 weeks (I, IV), and 3 weeks (II)	24 weeks	48 weeks	
I (rat)	121μm (±1.0)	120μm (±3.0)	116μm (±3.0)	within variation limits
II (rat)	83.6μm (±2.7)	85.7μm (±3.9)	84,5μm (±3.6)	within variation limits
IV (rabbit)	99μm (±3.0)	103μm (±3.0)	97μm (±5.0)	within variation limits

In the histological evaluation, in the early follow-up periods, individual filaments were seen as round cross sections of filaments, but at 48 weeks there were fissures or they were seen as spots of material. This was considered to be artefactual, probably having occurred during specimen processing, since there was no tissue in-growth from the surrounding fibrous tissue into the empty holes of the cracked filaments. PLDLA material was evaluated under polarized light and at 48 weeks the implant material was still polarizing.

5.3 Histological findings in subcutaneous PLDLA implants

After subcutaneous implantation of fibrous PLDLA implants in rats, fibrous tissue in-growth had proceeded from all sides of the implant, filling it completely within three weeks (Fig. 7). In all samples with incomplete tissue in-growth, the innermost fibrous tissue invasion front consisted of fibrin, followed by inflammatory cells and fibroblasts. The numbers of macrophages had increased clearly at three weeks postoperatively, and their presence seemed to increase throughout the whole follow-up period. The orientation of the fibrous tissue within the fibrous implant changed with time from being non-oriented, loose connective tissue into highly oriented, dense connective tissue, forming fibrous tissue septae (Figs 7–11). The septae appeared first between the bundles of PLDLA filaments, and later also between individual PLDLA filaments inside the PLDLA bundles. At the longest follow-up period of 48 weeks, there were highly oriented layers of dense connective tissue between PLDLA bundles and filaments (Fig.11).

The amount of dense connective tissue at 48 weeks did not differ in the three experimental groups of dense, ordinary and loose type implants, being 18%, 20% and 18%, respectively ($p = 0.8$). The amount of loose connective tissue were similar in the study groups of dense and ordinary implants (37% and 36%,

respectively), and were slightly higher in the group of loose type implants (49%), but the difference was not statistically significant ($p = 0.16$). Thus the difference in pore sizes between the implants with three different densities used in the current study did not have any effect on the type of tissue in-growth or the amount of dense connective tissue formation.

Tissue reactions around the knitted tubular mesh were similar to those seen with disc-shaped implants. The material became filled with loose connective tissue, and PLDLA fibers were surrounded by a layer of dense connective tissue that thickened with time.

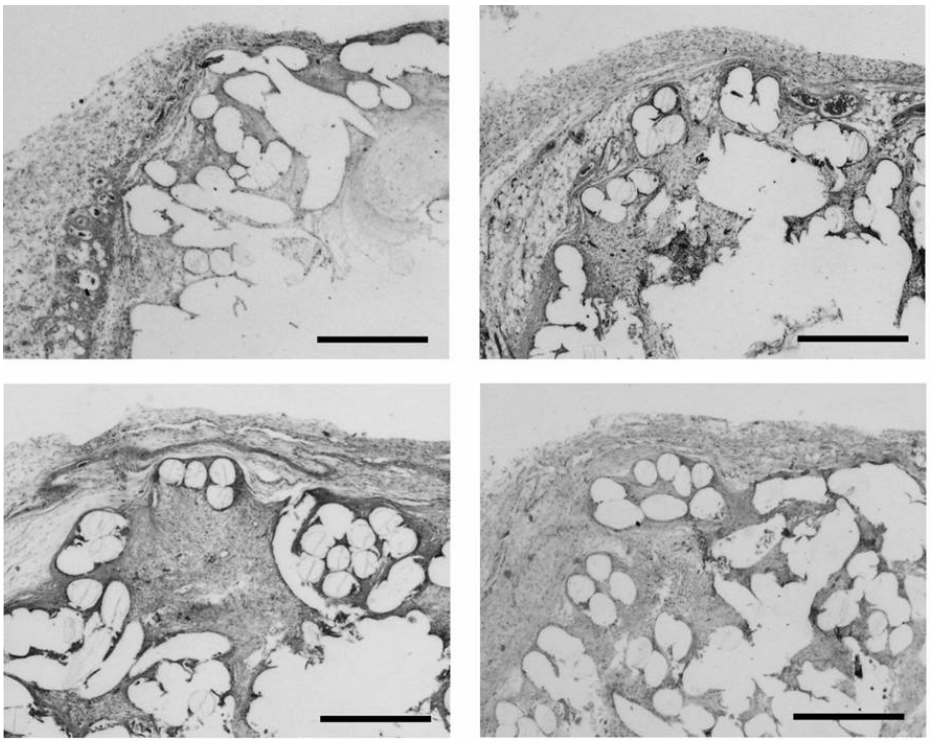

Fig. 7. Ordinary-type implants, stainings HE, scale bars 500µm. A) Three days postoperatively, tissue in-growth is incomplete. Fibrin, polymorphonuclear neutrophils, monocytes and some fibroblasts were present. B) At one week, tissue in-growth had proceeded further, but an acellular zone is seen in the middle of the implant. Fibroblasts had become attached to the surface of the filaments and in the edge some new capillaries had grown inside the implant area. C) At two weeks, the centre of the implant was still empty of cells. New capillaries within the implant had infiltrated deeper than one week previously. The amount of loose connective tissue

within the implant had increased and there were 1–3 layers of fibroblasts around each filament at the edge of the implant. D) At three weeks, the tissue in-growth has reached the center. Each bundle was surrounded by a thin layer of fibrous connective tissue, with 1–5 layers of fibroblasts. More layers were seen in the areas close to the surface of the implant than compared to the situation in the center.

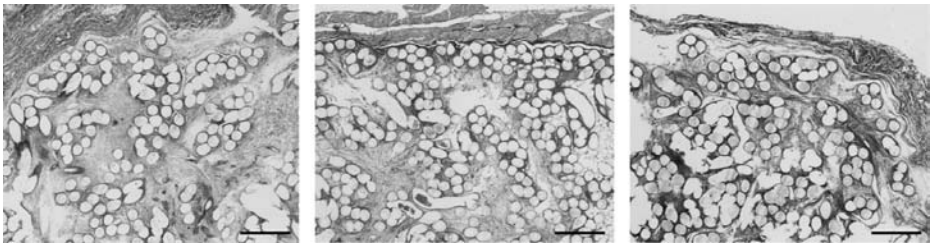

Fig. 8. PLDLA disc-shaped implant, 48 weeks postoperatively, stained with van Gieson, scale bar 500µm. A) Loose, B) Ordinary, and C) Dense-type implant. Dense connective tissue was highly oriented around single PLDLA filaments. The amount of fibrous tissue was higher in the areas close to the PLDLA filaments, less dense fibrous tissue appeared in the empty areas between fibers area, seen especially in loose-type of implants that have larger fiber-free areas. A number of capillaries were seen throughout the implants. The number of macrophages had increased clearly when compared to earlier follow-up samples. Material appeared to have artefactually fragmented by 48 weeks, but no tissue in-growth into the cavity of single filaments was seen in any samples.

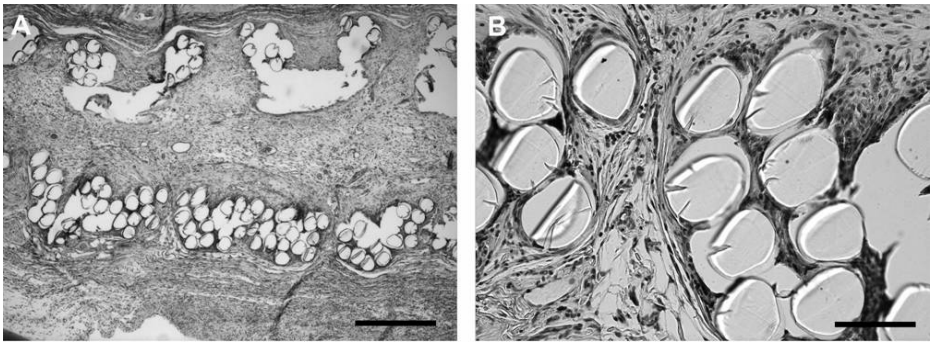

Fig. 9. Tubular mesh implant. At three weeks postoperatively, loose connective tissue had filled the lumen of the tubular knitted structure in the middle of the implant. Cells surrounded each PLDLA filament. The Fissures seen in individual PLDLA filaments are artefacts. Staining with HE, scale bars A = 500µm, B = 100µm.

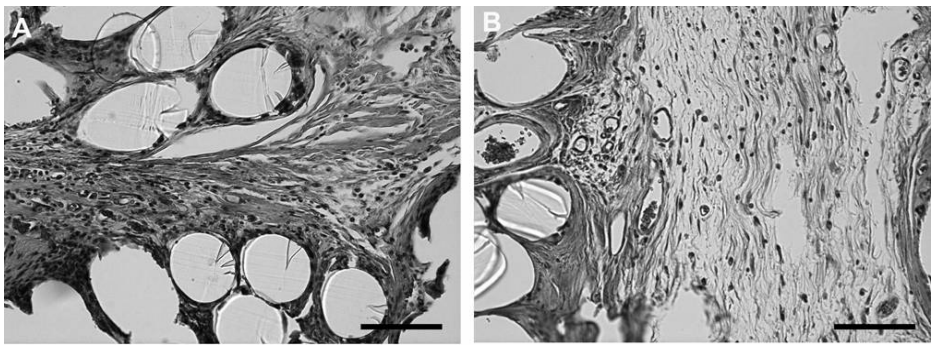

Fig. 10. At 24 weeks postoperatively, a layer of dense connective tissue had formed around PLDLA filaments, and cell density in immediate surrounding of each PLDLA filament has increased clearly. Staining HE (A), Van Gieson (B), scale bars 100µm.

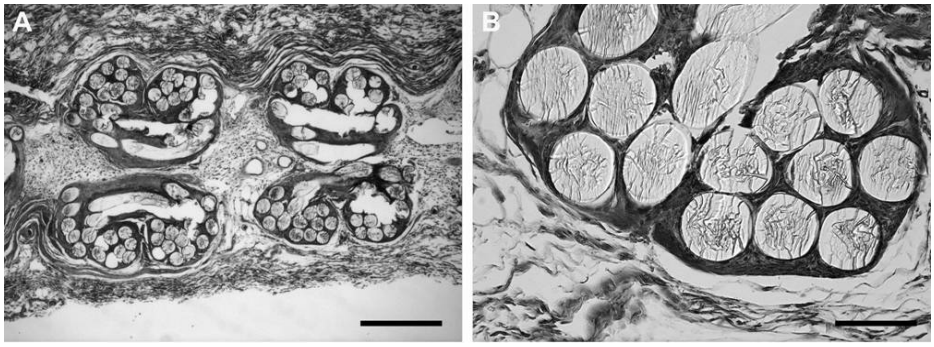

Fig. 11. At 48 weeks postoperatively, the PLDLA filaments are cracked. The cracking was thought to be an artefact since there is no tissue in-growth within the holes of polymer matrix. Tissue reactions occured just around each PLDLA filament. Staining Van Gieson, scale bars A = 500µm, B = 100µm.

5.4 FESEM studies of knitted tubular mesh implants

The FESEM studies of knitted tubular mesh implants revealed the material surface to be very smooth and the knitted structure maintained for 48 weeks (Fig 12). At 48 weeks, however, there was longitudinal fragmentation of the material with clear in-growth of cellular material into the cracks. The cut surface maintained its smoothness with sharp edges up to 36 weeks. At 48 weeks, the cut surface looked as damaged by the cutting knife indicating softening of the material. The cut surface of each filament was also longitudinally fragmented by

the cutting knife, also from the innermost part of each filament, as evidence of the loss of mechanical strength of the material (Figures 13–18).

Tissues around PLDLA filaments displayed an increase in the tissue layers around each filament with time. Dense tissue layers were seen at the longer follow-up period, with looser tissue structures further away from filament bundles.

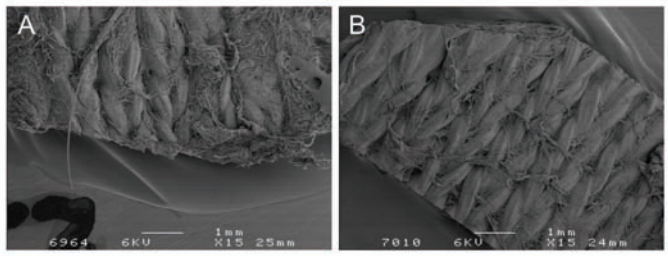

Fig. 12. FESEM micrograph of a tubular knitting made of PLDLA 96/4 fibres. A) The surface structure of the knitted PLDLA structure is clearly visible 12 weeks after implantation in rats' subcutis. B) After 48 weeks, the knitted structure is still visible.

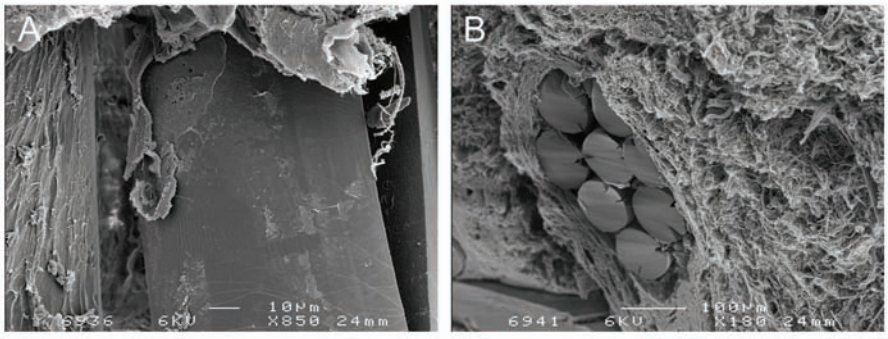

Fig. 13. FESEM micrograph of a PLDLA 96/4 implant, three weeks postoperatively. The tissues located on the material were removed during sample processing for better visualisation of the filament itself. A) The surface of the filament was smooth and tissue had attached to the surface. B) A thin layer of connective tissue is seen around the bundle of PLDLA 96/4 filaments. The amount of connective tissue was clearly lower inside a single PLDLA bundle, i.e. between individual PLDLA filaments.

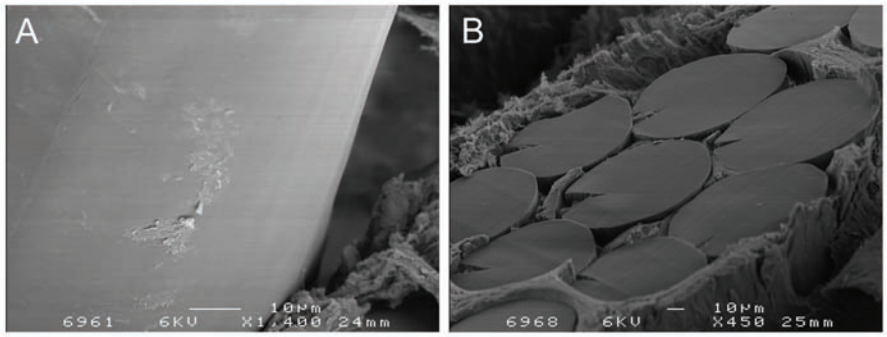

Fig. 14. FESEM micrograph of the surface of PLDLA 96/4 filaments, 12 weeks after implantation. A) The surface was still smooth. B) The amount of connective tissue had increased, with clear layers of connective tissue seen in the upper right corner. The cracks seen in PLDLA filaments are processing artefacts since there was no tissue ingrowth into these cracks.

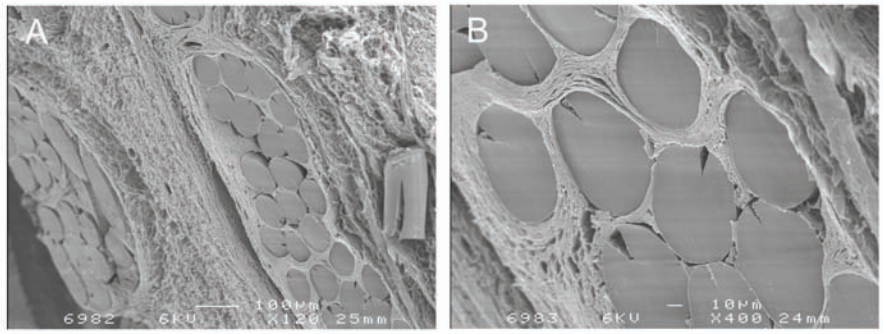

Fig. 15. FESEM micrograph of a PLDLA implant, 18 weeks postoperatively. A) The bundles of 8 PLDLA filaments forming a single fiber can be distinguished. In this figure, the fibrous tissue layer structure is visible just around each bundle, while the areas further away from the bundles are filled with connective tissue with a looser structure. B) Connective tissue filled the gaps found between individual PLDLA filaments. The layer structure of the connective tissue is clearly visible. The cracks in the filaments are artefacts.

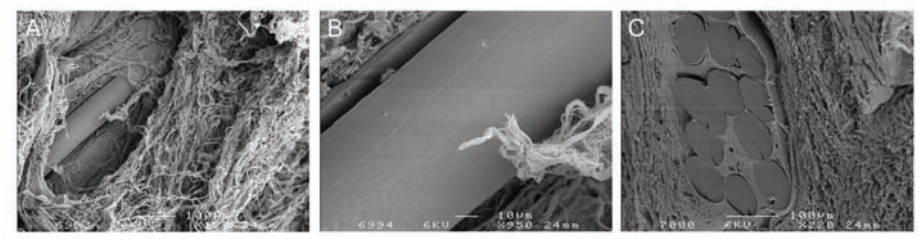

Fig. 16. FESEM micrograph of a PLDLA implant, 24 weeks after implantation. The surrounding tissues have been partly removed by stripping for better visualisation of the material itself. A) The surface of the material is still extremely smooth. There is a longitudinal crack in the filament but there was no tissue growth into the crack. B) Higher magnification of the previous figure. C) The layer structure of the connective tissue is visible adjacent to each bundle.

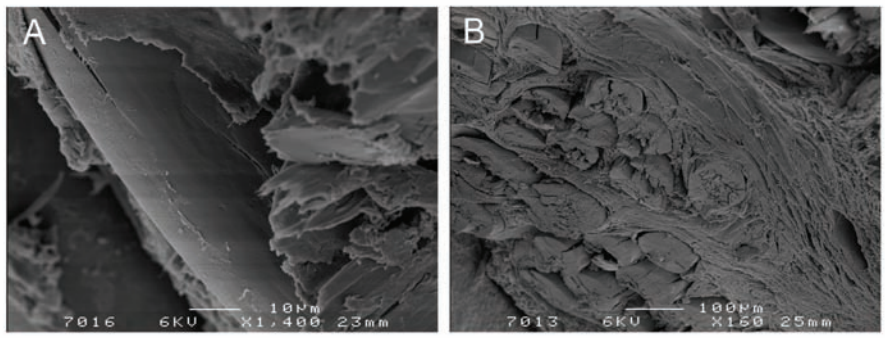

Fig. 17. FESEM of PLDLA filament bundle, 48 weeks postoperatively. A) The uncut surface material was still quite smooth. There were cracks in the filaments and in some cracks there was cellular material seen inside the cracks. B) The cracks were seen throughout the material, even in the center of a single filament. The cracks seem to have a longitudinal orientation.

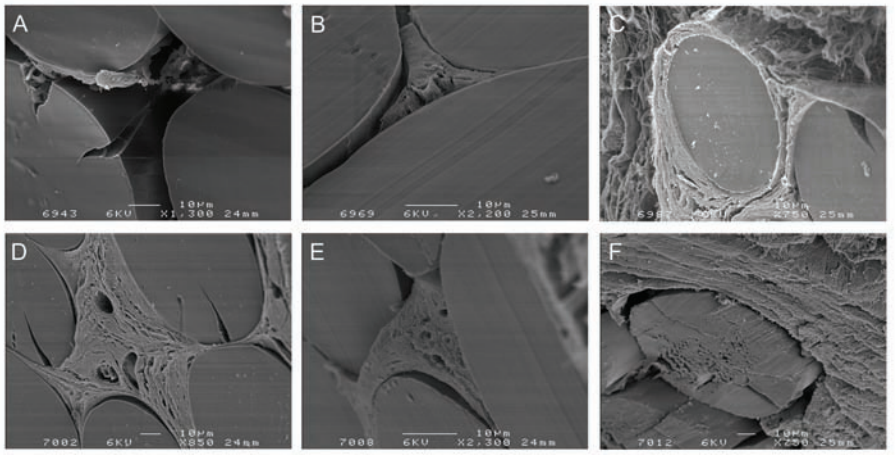

Fig. 18. A-F. FESEM micrographs of cut surfaces of PLDLA 96/4 filaments. A) 3 weeks, B) 12 weeks, C) 18 weeks, D) 24 weeks, E) 36 weeks and F) 48 weeks postoperatively. The cut surface of each PLDLA filament was smooth and boundaries were sharp up to follow-up period of 36 weeks. At 48 weeks post-implantation, the cut surface of PLDLA filament had become cracked throughout the material and the cut surface was damages by the cutting knife indicating softening of the material.

5.5 Soft tissue response to episcleral PLDLA implant in rabbits

Histologically, there were no implant fragments seen within sclera and there was no atrophy of sclera under the PLDLA implant in any sample. The amount of connective tissue inside the implant increased throughout the follow-up period, becoming more organized with time. The number of macrophages and foreign body giant cells increased with time, this being most probably related to more active material degradation at the longer follow-up points. All tissue reactions were very limited and located only within the implant area or in the immediately surrounding area. There were no inflammatory cells within the sclera or in the retinal layers. The structure of the retina and the cornea seemed to be normal in all samples during the whole follow-up period. The nonabsorbable suture material could be easily distinguished from fragments of PLDLA implants, and a foreign body type reaction similar to that seen around PLDLA implants was observed immediately around the sutures (Figures 19A-B, Figure 20 and Figures 21A-B).

There were no macroscopic changes of infections, but in four rabbit eyes, all with PLDLA implants, some evidence of infection were noticed on the histological samples. One reason for these infections might be associated with the

fact that we were using a new implant with which we had no prior experience. All four infections occurred among the first 17 rabbits, but in the last 31 operations not a single infection was noticed.

With respect to the silicone implants, a thin layer of connective tissue surrounded the implant, containing very few macrophages and lymphocytes but some capillaries close to the implant were seen, and the layer was similar in thickness or became thinner with time (Figures 19C and 21C).

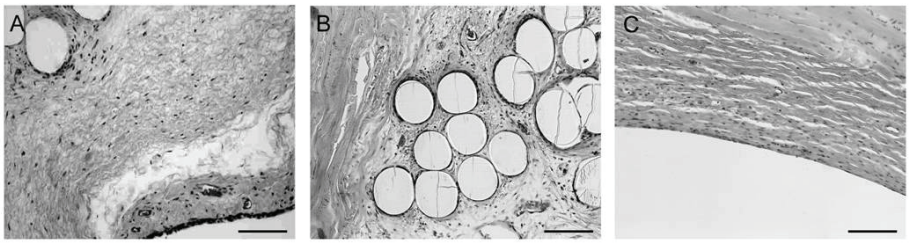

Fig. 19. Histological sections from episcleral implants at 1 month postoperatively. A) View from conjunctiva: inflammatory cells, mainly macrophages, can be seen only in the immediately surrounding areas of the implant filaments. B) View within a PLDLA 96/4 implant: a thin layer of fibrous tissue has been formed around each PLDLA 96/4 filament, with loose connective tissue and new capillaries in the areas between filaments. C) View from a thin capsule around a silicone sponge implant. Some inflammatory cells, fibroblasts and a thin layer of connective tissue can be seen. (Stainings HE, scale bars 100µm).

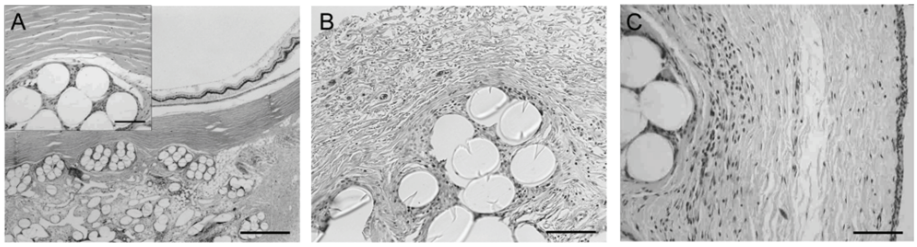

Fig. 20. Histological sections with HE stainings at 5 months postoperatively. A) View of PLDLA 96/4 filaments on the sclera: despite macrophages and other inflammatory cells just around PLDLA 96/4 filaments, there were no inflammatory cells within the sclera (scale bar 600µm). Higher magnification shows the sclera (scale bar 100µm). B) and C) inflammatory cells were in the area closely surrounding PLDLA 96/4 filaments. Further away on the conjunctiva, the number of inflammatory cells declined (scale bars 100µm).

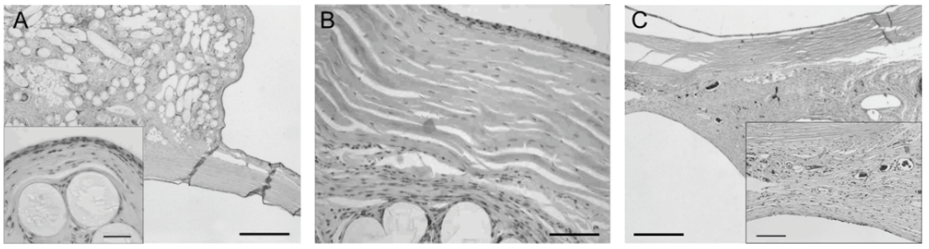

Fig. 21. Histological sections at 48 weeks postoperatively A) Some multinucleated foreign body giant cells seen on the surface of PLDLA 96/4 filaments (staining HE, scale bar 600µm). With higher magnification, each PLDLA 96/4 fiber is surrounded by a thin layer of fibrous tissue. In this sample, the conjunctiva is located very close to the implant filaments (staining HE, scale bar 50µm). B) No inflammatory cells were seen within the sclera (staining HE, scale bar 100µm). C) A thin layer of smooth fibrous capsule surrounds the cavity of the silicone sponge. (staining HE, scale bar 600µm). Higher magnification shows details of the capsule (staining HE, scale bar 100µm).

5.6 Indentation depth with PLDLA implants vs. silicone sponge implants in rabbits

It was noted that the indentation achieved with the PLDLA implant (diameter of 3–3.5mm) was lower than that obtained with the silicone sponge implant (diameter of 4mm). The mean indentation depth in the whole study period was 2.14mm (SD 0.18mm) in the PLDLA group and 2.46mm (SD 0.18mm) in the silicone group ($p < 0.001$). The difference in depths was apparent from the beginning and it remained constant throughout the follow-up period.

It was also observed that the depth of indentation decreased over time in both groups at comparable rates. The average decrease from the beginning to 5 months was 0.45mm (SD 0.21mm) in the PLDLA 96/4 group and 0.39mm (SD 0.11mm) in the silicone group ($p = 0.4$). The diameter of the bulbus increased on average by 1.23mm (SD 0.26mm) in the PLDLA 96/4 group and by 1.21mm (SD 0.22mm) in the silicone group ($p = 0.8$) (Figure 22).

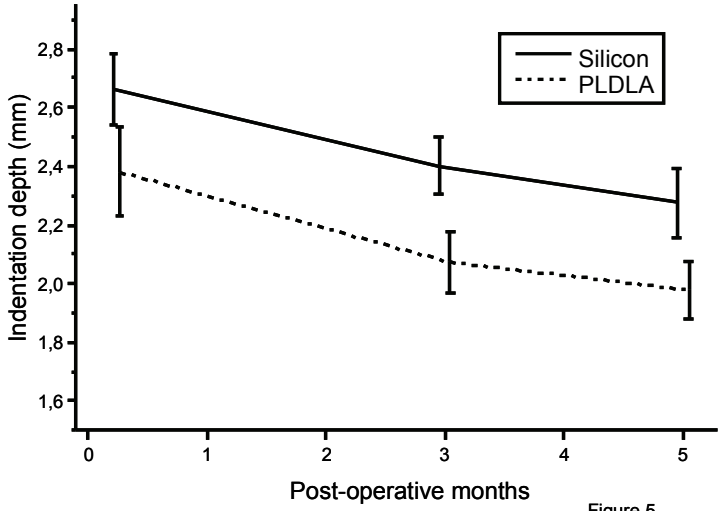

Figure 5
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Fig. 22. Means of indentation depths with 95% confidence intervals. The indentation achieved was lower with PLDLA 96/4 implants from the beginning, most probably as a result of the difference in the size of the implants and the difference in tightening of the sutures, since the materials were not similar in their handling properties. The indentation depth decreased similarly over time in both groups. The average decrease from the beginning to 5 months was 0.45mm (SD 0.21mm) in the PLDLA 96/4 group and 0.39mm (SD 0.11mm) in the silicone sponge group (p = 0.4).

6 Discussion

Scleral buckling is a commonly used method for the operative treatment of RRD. During the scleral buckling procedure, the implant is tightly sutured either episclerally or intrasclerally and therefore a precise location can be assured and sustained securely. It is also possible to check the location and degree of indentation during the operation. Nonabsorbable implant materials may cause long-term complications during postoperative years. By using bioabsorbable synthetic materials the benefits of scleral buckling operations may be achieved without the long-term complications that can be seen with permanent implants (Schepens & Acosta 1991). Modern synthetic bioabsorbable materials can be prepared to be slowly degrading, and be manufactured into different sizes and shapes. They can be used in patients with uncomplicated rhegmatogenous retinal detachments since the need for implantation is only temporary and all surgical treatment should aim at the best possible clinical result with the least possible morbidity (Schepens & Acosta 1991, Kreissig *et al.* 1992, Lincoff & Kreissig 2000).

Any complication related to foreign material may require the inconvenience of a reoperation for removing the implant. Implant removal rates of 3.2% and 3.8% have been reported (Hilton & Wallyn 1978, Deutsch *et al.* 1992) Removal operation itself has been considered to pose a risk for redetachment. The risk rate has earlier been stated to range from 1.3% to 47% (Russo & Ruiz 1971, Hilton & Wallyn 1978, Lindsey *et al.* 1983). In the latest studies the redetachment rate after implant removal has been reported to be 8.2% and 8.6% (Deutch *et al.* 1992, Deokule *et al.* 2003). The risk may be higher if the retinal breaks were not found in the primary operation (Deutch *et al.* 1992). The duration of the implantation was not related to the redetachment risk (Deutch *et al.* 1992, Deokule *et al.* 2003). The risk was higher within the first six months after implant removal operation (Deokule *et al.* 2003). However, it must be remembered that there is a risk for late recurrence of the retinal detachment even without any removal operations, with risk rates reported between 2.2% (Foster & Meyers 2002) and about 6% (Kreissig *et al.* 1992). The redetachments requiring reoperation can be caused by a new retinal break(s), by opening of the original break(s) or they may have developed due to proliferative vitreoretinopathy.

Even though scleral buckling operations have been performed since 1949, there is still no consensus about the optimal duration of indentation in rhegmatogenous retinal detachment. The minimum time period recommended by

the American Academy of Ophthalmology for determining the functional success (measured as best corrected visual acuity) is six months (American Academy of Ophthalmology 1996). Many biological synthetic materials have been used for creating temporary indentation with variable durations of indentation. Lincoff`s balloon has been used for creating a temporal buckling effect with the duration of implantation of only 1–2 weeks, and yet the (primary) retinal attachment rate has been 93% (Kreissig *et al.* 1989). In limited local detachments with only one retinal break, an over 90% attachment rate has been achieved after a single operation and 99% after reoperation (Lincoff & Kreissig 2000). In the study of Kreissig et al, in 107 patients after minimal local buckling operation with follow-up of 11 years, PVR was the most common reason for early redetachments, while new retinal holes were the main cause for late redetachments (Kreissig *et al.* 1992). In such cases, a reoperation was successfully performed in all patients (using a temporary balloon in 50%), which indicates that a local minimal surgery is sufficient and can be safely performed repeatedly. These authors did not observe any prophylactic value of permanent cerclage for preventing redetachments (Kreissig *et al.* 1992). These results indicate that simple rhegmatogenous retinal detachments do not necessary need a permanent buckling effect and a bioabsorbable scleral buckling implant with suitable mechanical properties could be used.

6.1 Experimental models and materials used in this study

The experimental models used in this study were subcutaneous implantation in rats and episcleral implantation on rabbits. The subcutaneous model was chosen since it provides information of local reactions in soft tissues. The model also provides easy access to the implantation area with minimum surgery and sample removal is technically easy to perform without harming the fibrous implant at the end of each follow-up period. Episcleral implantation was chosen since it gives important information about local tissue reactions in tissues where the implants will be used. The rabbit was chosen due to the sufficiently large size of the eye, allowing performance of the operation with similar techniques as used in human eyes. The sclera in rabbits is thinner than the human sclera, but the pliability was quite similar. Thus comparing the results of the indentation creating properties achieved in rabbits to humans is possible.

The implants used in this study were prototypes, specially developed and prepared aiming at fulfilling the requirements needed in scleral buckling

operations. The demands for special application in surgery are important factors which need to be taken into account when developing new implants. The desired properties for non-absorbable materials used for scleral buckling have been previously believed to be softness and elasticity for preventing scleral erosion or exposure through conjunctiva. In addition, it was considered that the material should not contain dead spaces because that kind of structure could lead to an increased risk of infection, and there should be possibility to load an antibiotic inside the material (Tolentino *et al.* 1981). Since the area available for operation is limited and large implants may cause ocular motility problems, the implants should be small in diameter and the shape should be such that it causes a good inward pointing indentation effect but would be as flat as possible outwards. This requirement has spurred the development of silicone sponge implants with oval and asymmetric diameters (Scholda *et al.* 1999). It is important that the scleral buckling implant can be tightly and securely attached onto bare sclera for creating and maintaining the precise location of indentation, and also preventing scleral erosion due to micromovement of the implant. In general, because the eye is slightly yielding, the shape of scleral surface is round and the surrounding conjunctiva is sensitive to pressure, the material should not be stiff and unyielding. The material should be mechanically sufficiently strong to be used episclerally, easy to handle and be histologically well tolerated. Sufficient indentation should be maintained for months rather than weeks. In addition, creation of fibrous tissue around (solid) implant has been considered to be beneficial since this could strengthen the underlying sclera (Tolentino *et al.* 1981). The implant should be available commercially in many sizes and shapes. The material should not cause adhesions to the ocular muscles and it should be non-antigenic (Schepens & Acosta 1991). Based on the results with hydrogel implants, it seems that extensive swelling of the material is also undesirable.

An implant with a fibrous structure made of PLDLA was developed to meet these requirements. Mechanically strong bioabsorbable fibers can be manufactured and further processed as a raw material for incorporation into woven or braided three dimensional structures. PLDLA 96/4 was chosen as the raw material due to previous good results with solid implants (Peltoniemi *et al.* 1999, Bergsma *et al.* 1995b, Cordewener *et al.* 1995). We chose a tubular structure with manually filled loose fibers to these prototypes to identify tissue reactions to the material itself. However, it is not possible to use this kind of structure in commercial products due to their variability, which was seen even macroscopically. Further development is needed for determining a suitable

manufacturing technique for creating the kind of structures which could possibly be prepared on a commercial scale.

6.2 Tissue reactions caused by fibrous PLDLA 96/4 implants and material degradation rate

The implants made of PLDLA fibers increase the proportional surface area of the implant. This may increase tissue reactions, including fibrous tissue formation. Bioabsorption of the polymer may also be enhanced since there is a large surface area available for hydrolyzation. Thus, it was considered especially important to study tissue reactions to the fibrous PLDLA implant.

We tested the subcutaneous fibrous implants at three densities but there was no difference in the rate of tissue in-growth or in the amount of dense connective tissue developing during the follow-up of 48 weeks. This can probably be explained by the fact that the minimum porosity that allows fibrous tissue cell migration was achieved with even the tightest “Dense-type” implants. The pores in the fibrous implants were large enough, they probably did not restrict tissue in-growth, and cells were free to invade the implants. The in-growth of small capillaries was also possible inside the implant pores. Subsequently, the difference in the pore size between the disc-shaped implants did not seem to have any effect on the rate of tissue in-growth. These results also indicate that a slight variation in the amount of PLDLA fibers within the implants may not have a major effect on the extend of tissue reactions.

Histologically, good tolerance of the fibrous implants was seen both in subcutaneous rat tissues and in the episclerally implanted versions in rabbit eyes. The amount of fibrous tissue inside the implant increased throughout the follow-up period, becoming more organized and showing septae over time. All tissue reactions were very limited and occured only within the implant area or in the immediately adjacent areas. After episcleral implantation, the sclera was intact and no inflammatory cells were seen within the sclera or in the retinal layers. The increase in the number of macrophages and foreign body giant cells is most probably related to the increasing material degradation and can be considered as a normal reaction to the bioabsorbable material used in this study, although no appreciable biodegradation at the light microscopical level could be demonstrated. In FESEM studies, it was found out that the material maintained the knitted structure at the macroscopic level for the whole follow-up period of 48 weeks. The material surface of each filament was very smooth and the surface structure

maintained until 36 weeks. The cut surface of each PLDLA filament was also smooth, with sharp boundaries at edges of the material present up to 36 weeks. However, by 48 weeks longitudinal fragmentation of the material and clear in-growth of cellular material into the cracks were seen. This indicates that the phase of the loss of material integrity had just started, although it was not visible macroscopically or even at the light microscope level. The material seemed to degrade first by cracking longitudinally, which means cracking along the longitudinally oriented PLDLA molecular chains. By 48 weeks the cut surface of the PLDLA filament was damaged by the cutting knife, indicating softening of the material.

This preliminary study was limited to 48 weeks. At this time total bioabsorption of the implant was not seen. Degradation of the material had started, as can be judged by the increasing number of macrophages and their swollen appearance, but the volume of single fibers in light microscopical level had not yet diminished. The material is known to be totally bioabsorbable and degradation takes place by hydrolytic scission of ester bonds in the polymer. Subsequent degradation of material will proceed when the material is absorbed by inflammatory cells, mainly macrophages and foreign-body giant cells. The molecules and particles of material are absorbed and used in cellular metabolism in the citric acid cycle (Törmälä *et al.* 1992). Absorption rate varies with the type of implant, but complete bioabsorption of PLDLA 96/4 plates in 2 years has been reported (Peltoniemi *et al.* 1999). When in the form of a fibrous structure, the biodegradation may take less than 2 years because of the relatively high proportional surface area exposed to degradation by hydrolysis. In the future, a longer study will be needed to determine the time period required for total bioabsorption of these fibrous implants.

6.3 Fibrous PLDLA 96/4 implant for scleral buckling

In this study, computerized tomography (CT) was used to measure the indentation effect of episcleral implants. CT is easy to perform and represents a very accurate radiological evaluation method which can be used to measure the small indentation depths caused by episcleral implants. Visualisation of anatomical details of the bulbus is possible. Imaging time is short, which reduces the effects of moving artefacts. The diameter of the bulbus during the follow-up periods of one week, and three and five months had increased only by 1.1mm. Therefore,

comparisons could be done between the measurement results at these three points in time.

An adequate indentation effect was achieved in both experimental groups (PLDLA vs. silicone sponge). There was a difference in the indentation depth between the two groups already at one week postoperatively. The reason for this is most probably the difference in the original size of the implants (diameter 3–3.5mm of PLDLA implants vs. 4.0mm of silicone sponge implants). It was also noted that the depth of indentation decreased similarly in both groups over time. This phenomenon has also been reported in previous studies, and it seems that 70–75% of the original indentation remains with non-absorbable implants after the reduction plateaus in the first postoperative year (Stone *et al.* 1977, Irvine & Stone 1981, Theodossiadis *et al.* 1994).

Handling of the PLDLA implant used in this study was different from that of the silicone sponge implant, since it was not as compressible. Consequently, tightening of the sutures over the implant was not as straightforward as with the silicone sponge implant. The silicone implant was cut with scissors and the PLDLA implant was reduced in size (from 3cm to 1cm in length) in the operation room with a hot wire loop. The hot wire loop was used because scissors may result in fraying of the fibrous PLDLA implant which was filled with a loose bundle of fibers. A hot wire loop is easy to use and it is commonly utilized for example in craniofacial surgery for cutting the edges of screws (Peltoniemi *et al.* 2002). A pre-knowledge of these material properties makes this process more manageable.

The complications that arose with this new device were a few infections in rabbits with episcleral implants. A total of four cases of infection were seen with the PLDLA implant. One reason for these infections might be associated with the fact that it is a new implant and we had no prior experience of its use. All four infections occurred among the first 17 rabbits, but in the subsequent 31 operations we did not encounter a single infection. However, these complications indicate that more experimental work is needed to evaluate this material when used for episcleral applications. It is also possible to produce infection-resistant ophthalmological implants using antibiotic-releasing bioresorbable material (Niemelä *et al.* 2006).

The PLDLA implant used in this study evoked an inflammatory tissue reaction around implant material. The reaction was localised and did not infiltrate the sclera. Previously, a localised inflammatory reaction and fibrous tissue formation have been detected also with other materials used for scleral buckling.

The local inflammatory reaction around the silicone sponge is generally mild and changes with time into a dense fibrous capsule containing a few vessels and occasionally some mononuclear cells (Vogel 1978, D´Hermies *et al.* 1998, D´Hermies *et al.* 1999a). Sometimes a foreign body granulomatous reaction has also been seen (Wilson & Green 1987). Despite these local tissue changes, the silicone implants are usually well tolerated (D´Hermies *et al.* 1999a). Clinically, problems due to local inflammatory reactions are seen after extensive tissue damage during the operation, such as after scleral resection operations and as side-effects of cryotherapy and diathermy, which both may cause tissue swelling, exudative fluid accumulation and necrosis (Aaberg & Pawlowski 1972, Lincoff & Kreissig 2000). Adverse reactions after scleral resection, diathermy and cryotherapy are probably related to direct tissue damage to sclera and/or chroioidea and/or retina.

Previously hydrogels have evoked long-term complications due to swelling of the material (as much as 185% volume increase) (Oshitari *et al.* 2003). These problems were attributable to the direct volume increase and cannot be considered to be caused by a local tissue reaction. In the clinical study of Roldan-Pallarés and Awad-el Susi, no complications were associated with episcleral implants made of porous PTFEe (Roldan-Pallarés & Awad-el Susi 2000). However, in that study the tissue reactions were not studied. In an experimental study, a nonabsorbable silicone band coated with porous e-PTFE evoked massive adhesions to conjunctiva and local microcalcifications were found (Mortemousque *et al.* 2001, Mortemousque *et al.* 2002). The adhesions were considered to be attributable to the roughness and hydrophilicity of e-PTFE, causing a continual stimulus and increasing the inflammatory reactions. The authors` estimation of the cellular response was that “It did not seem to influence the potential buckling properties of the material and did not produce any toxic effects on the surrounding tissues. By itself, this reaction does not exclude the possible use of this material for scleral buckling procedures” (Mortemousque *et al.* 2002). It is also worth noting that in that study the chronic granulomatous tissue reaction was found only in histological samples and no clinically significant inflammatory reaction was detected. It must be remembered that those implants were non-absorbable and thus permanent. The reactions around a permanent implant need to be even milder than those seen around bioabsorbable materials, since these reactions may persist for the entire implantation period. The material of fibrous PLDLA implants used in this study did not show any swelling by at 48 weeks, i.e. the diameter of single filaments had not changed.

Biological materials, whether tissue transplants or prepared materials, are bioabsorbable and evoke an inflammatory reaction (L´Esperance 1966, Cibis & Knobloch 1967, Vygantas & Kanter 1974, Regenbogen *et al.* 1976, Francois *et al.* 1979). Usually the chronic inflammatory reaction is mild, temporary and well tolerated. It seems that the inflammatory reaction caused by the scleral buckling material itself does not cause any additional problems to the healing of retinal detachment. The healing is mostly dependent on the success in treating the original cause of detachment, which means closing the retinal break(s) for a sufficiently long time. Thus, tissue reactions caused by episclerally placed materials do not seem to have any major impact on healing of the retinal detachment as long as the material creates an indentation that closes the retinal break(s) for a sufficiently long period of time, does not swell excessively and is soft and moldable enough, and does not cause scleral erosion or conjunctival thinning. However, tissue reactions are of importance when considering patient comfort and late events. After reattachment of the retina, the implant is no longer necessary, but with permanent materials the implant in most cases still exists along with the risk of long term complications. Therefore a nonabsorbable material should cause minimal tissue reactions for the whole implantation period, which may be decades. With bioabsorbable materials the implant is only temporary, as are also the tissue reactions caused by the material and its degradation process. After the material has degraded and been absorbed by host tissues, there will be complete resolution of the inflammatory reaction and there is no possibility of implant related complications. With bioabsorbable materials, the tissue reactions are especially important during the initial healing process, which in retinal detachment surgery occurs during the first months, and then during the late degradation phases of the material.

In the fibrous PLDLA implant used in our study biodegradation took more than 48 weeks. This suggests that postoperative tissue healing (during the first postoperative weeks), and retinal reattachment with scar formation (during the first postoperative months) occur before biodegradation of the implant material (after 48 weeks) (Lincoff *et al.* 1981). Actually, biodegradation could occur sooner than 48 weeks postoperatively, even as soon as 6 months postoperatively, since scar formed by the cryoprobe during the surgery matures during the first postoperative months keeping the retina attached thereafter.

Further studies are needed for evaluating these materials in clinical use and evaluating the suitability of these kinds of bioabsorbable implants as aids in scleral buckling in the surgical treatment of retinal detachment.

7 Conclusions

On the basis of the results, the following conclusions can be drawn:

The biocompatibility of a fibrous implant made of PLDLA 96/4 fibers placed subcutaneously is good in the follow-up of 48 weeks despite relatively high surface area of the material. The material was not bioabsorbed within 48 weeks.

The PLDLA 96/4 buckling implant (implant diameter of 3–3.5mm) used in this study created a lower indentation than the corresponding silicone sponge implant (implant diameter of 4mm). The achieved indentation decreased in both groups in a comparable manner over the follow-up period of 5 months.

Histologically, tissue reactions were very limited and located only within the implant area or in the immediately surrounding areas. The sclera was intact and no inflammatory cells were seen within the sclera or in the retinal layers. Thus, good tissue tolerance was seen to the episclerally sutured implant made of fibrous PLDLA 96/4.

The duration of the indentation effect was sufficient to be used as scleral buckling implant in retinal detachment surgery in uncomplicated cases.

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