



SUSANNA LAAKSOVIRTA

Biodegradable, Self-reinforced, Self-expandable
Lactic and Glycolic Acid (SR-PLGA 80/20)
Copolymer Spiral Prostatic Stent

Analysis of Mechanical and Biological
Properties and Clinical Results



ACADEMIC DISSERTATION

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original papers, referred to in the text by their Roman numerals (I-V).

I Välimaa T, Laaksovirta S, Tammela TLJ, Laippala P, Talja M, Isotalo T, Petas A, Taari K, Törmälä P (2002): Viscoelastic memory and self-expansion of self-reinforced bioabsorbable stents. *Biomaterials* 23(17): 3575-82.

II Laaksovirta S, Välimaa T, Isotalo T, Törmälä P, Talja M, Tammela TLJ. Encrustation and strength retention properties of self-expandable, biodegradable self-reinforced L-lactide-glycolic acid copolymer 80:20 spiral urethral stent in vitro. *J Urol* (in press).

III Laaksovirta S, Laurila M, Isotalo T, Välimaa T, Tammela TLJ, Törmälä P, Talja M (2002): Rabbit muscle and urethral *in situ* biocompatibility properties of the self-reinforced L-lactide-glycolic acid copolymer 80/20 spiral stent. *J Urol* 167(3):1527-1531.

IV Laaksovirta S, Talja M, Välimaa T, Isotalo T, Törmälä P, Tammela TLJ (2001): Expansion and bioabsorption of the self-reinforced lactic and glycolic acid copolymer prostatic spiral stent. *J Urol* 166 (3): 919-922.

V Laaksovirta S, Isotalo T, Talja M, Välimaa T, Törmälä P, Tammela TLJ (2002): Interstitial laser coagulation and biodegradable self-expandable self-reinforced poly-L-lactic and poly-L-glycolic copolymer spiral stent in the treatment of benign prostatic enlargement. *J Endourol* 16 (5): 311-315.

ABBREVIATIONS

AUR	Acute urinary retention
BPE	Benign prostatic enlargement
BPH	Benign prostatic hyperplasia
CEN	Comite Europeen de Normalisation
Ch	Charriere'
DAN-PSS1	Danish Prostate Symptom Score 1
F	French
HIFU	Transrectal high-intensity focused ultrasound
ILCP	Interstitial laser coagulation of the prostate
ISO	International Organization for Standardization
IUC	Intraurethral catheter
LUTS	Lower urinary tract symptoms
PGA	Polyglycolic acid
PLA	Polylactic acic
PLA 96L/4D	Poly-L,D-lactic acid
PLGA 80L/20G	Polylactic-glycolic acid
PLLA	Poly-L-lactic acid
SEM	Scanning electron microscope
SR	Self-reinforced
TUMT	Transurethral microwave therapy
TUNA	Transurethral needle ablation of the prostate
TURP	Transurethral resection of the prostate
TUVP	Transurethral vaporization of the prostate
UTI	Urinary tract infection
VLAP	Visual laser ablation of the prostate

INTRODUCTION

The use of metallic and plastic stents in surgery is fraught with a number of drawbacks. Above all device-related urinary tract infections and the development of encrustation on material surfaces are common complications associated with urinary catheters and stents. These problems can cause significant patient morbidity and are the major factors limiting long-term use of devices within the urinary tract (Baert et al 1993, Löser and Fölsch 1996, Peng et al 1996, Pescatore et al 1997).

Biodegradable, self-reinforced spiral stents are the latest promising innovation in the field of temporary supporting devices in surgery, and since 1993, when the first biodegradable self-reinforced PLLA (poly-L-lactic acid) urethral stent was introduced, the development of new materials and configurations of urological stents has been rapid. An ideal stent would provide adequate support to a duct wall such as, like the urethra, would maintain the lumen open during and after the healing process and bioabsorb from the body. The material must fulfil certain biocompatibility demands stipulated in the guidelines for tissue biocompatibility analysis and risk assessment for clinical use of new medical devices. The rigidity of the material must be suited to the operating target, the degradation products must also be metabolically biocompatible and the rate of degradation suitable for tissue regeneration. Devices must also have good sterilization properties.

Biodegradable urethral stents have been used clinically with good results in the prevention of postoperative urinary retention after visual laser ablation of the prostate (VLAP) (Talja et al 1995, Petas et al 1997a, Petas et al 2000) and transurethral microwave therapy (TUMT) (Dahlstrand et al 1997, Devonec and Dahlstrand 1998). Biodegradable stents have also been used with endoscopic urethroplasty with a free skin graft on a resorbable stent to treat 2 - 4 cm-long bulbar urethral strictures with a minimal invasive technique (Oosterlinck and Talja 2000, Isotalo et al 2000).

Petas and coworkers (1997b) concluded that the 6-month's degradation time of the SR-PLA 96/4 lactide copolymer spiral stent was unnecessarily long compared with the duration of prostatic swelling and tissue sloughing after visual laser ablation of the prostate. On the other hand, the previously tested self-reinforced, self-expandable polyglycolic-acid (SR-PGA) stent used in preventing postoperative urinary retention and avoiding the need for prolonged catheterization after interstitial laser coagulation of the prostate proved to be an effective and safe device, but in some cases, the degradation time of 3 to 4 weeks was too short (Petas et al 2000).

A need was thus perceived to manufacture a stent from a new copolymer, which would optimize the degradation time to about 2 months and be suitable for clinical use after procedures inducing prostatic oedema postoperatively.

The aims of the present study were to evaluate the biocompatibility, viscoelastic memory and mechanical and expansion properties of a new biodegradable material *in vitro* and *in vivo* and to evaluate the efficacy of biodegradable SR-PLGA 80/20 stents clinically in a pilot study treating benign prostatic enlargement (BPE) with minimally invasive ILCP (interstitial laser coagulation of the prostate) thermotherapy.

REVIEW OF THE LITERATURE

1. BIODEGRADABLE MATERIALS

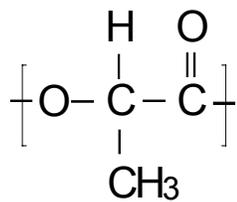
The first significant indication for bioabsorbable polymers was their use as surgical suture material, introduced in the 1960s. Polylactic acid (PLA) suture material was first adopted by Kulkarni and coworkers (1966). In 1967, Schmitt and Polistina developed the manufacture of polyglycolic acid (PGA) sutures. The first commercial suture, Dexon® (glycolic acid/lactic acid copolymer), was available in 1970 and since then there has been intensive development of medical devices made of bioabsorbable polymers (Gilding and Reed 1979). The use of biodegradable devices in the fixation of fractures of long bones was suggested by Schmitt and Polistina (1969) and first used clinically in Finland in 1984 (Rokkanen et al 1985). The development of biodegradable devices for urological use started in Finland in the late 1980s as a result of encouraging experimental and clinical experience, mainly in the field of orthopaedics, with bioabsorbable implants (Mäkelä 1989, Hirvensalo 1990, Törmälä 1992, Rokkanen et al 1985, 1992 and 1996).

1.1 Polyglycolic acid (PGA)

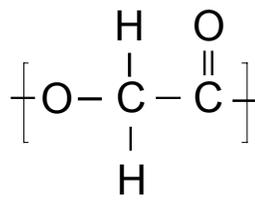
Polyglycolic acid is the simplest aliphatic polyester. It is synthesized by ring opening polymerization from glycolide, resulting in a poly-alpha-hydroxy derivate (Gilding and Reed 1979). The glycolic acid molecule has no chiral centre and therefore no enantiomers are not formed. Polyglycolide is polymerized from a glycolic acid dimer (Taylor 1987, Streitweiser et al 1992) (Table 1).

1.2 Polylactic acid (PLA) and poly-L,D-lactic acid (PLA 96/4)

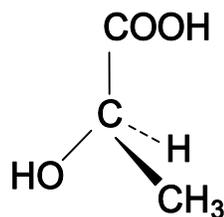
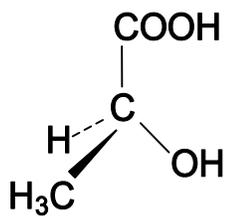
Polylactic acid is one of the poly- α -hydroxy acids and belongs to the group of aliphatic polyesters like PGA. Polylactide is polymerized from a lactic acid dimer. Lactic acid possesses an asymmetrically substituted carbon atom and is encountered in two enantiomeric forms, L(+)-lactic acid and D(-)-lactid acid. In the Fischer projection, with the carbon chain vertical and the carboxyl group at the top, the D enantiomer has the hydroxyl group on the right hand side (Taylor 1987, Mälkönen 1989, Daniels et al 1990). The two enantiomers differ significantly from each other in rate of biodegradation (Cutright et al 1974). Copolymers with molecular chains consisting of repeating units of both of these monomers can be polymerized. The degradation rate and amorphous sections of this type of random copolymer increase when the proportion of D-lactide increases from 0 to 50 % (w/w) (Kulkarni et al 1971). PLA 96/4 is a polymer of L- and D-lactid with a ratio of 96/4 L- and D-lactic acid respectively. The physical properties of the copolymers depend on the relative amounts of the L and D configurations (Vert et al 1992), (Table 1).



PLA



PGA



+LACTIC ACID (L) -LACTIC ACID (D)

Figure 1. PLA and PGA monomers and L- and D-enantiomers of PLA.

Name of copolymer	Abbreviation	Degradation time	Degradation time
		In vitro	In vivo
Polyglycolic acid	PGA	3-4 weeks	3-4 weeks
Poly-L-lactic acid	PLLA	12 months	8-10 months
Poly-L,D-lactic acid	PLA 96/4	30 weeks	5-6 months
Poly-lactic-glycolic acid	PLGA 80/20	2 months	2-3 months

Table 1. *In vitro* and *in vivo* degradation times of different poly- α -hydroxy acid polymers.

1.3. PLA:PGA Copolymers

The polymerization product of lactic acid (PLA) and glycolic acid (PGA) is a copolymer of these α -hydroxy acids. In Vicryl®, the first commercially available copolymer of polylactic and polyglycolic acids the ratio of PLA/PGA was 92/8 (Gilding and Reed 1979) (Table 1).

In this study the PLA/PGA ratio was 80/20. An increase in the amount of PGA accelerates the degradation of the copolymer.

2. PROCEDURE FOR SELF-REINFORCING BIODEGRADABLE POLYMERS

Partially crystalline, linear-chain absorbable polymers evince only modest mechanical strength values when manufactured by nonreinforcing techniques (Vainionpää et al 1989). To ensure the good mechanical properties required of a material for urological spiral stents self-reinforced (SR) PGA, PLGA80/20 and PLA wires have been devised by means of extrusion and solid-state drawing techniques (Törmälä 1992). Self-reinforced materials have been manufactured by die-drawing, where by long polymer molecules become parallel, forming microfibrils in the polymer matrix. The filamentous material and matrix have thus the same chemical composition. When part of the microstructure is oriented into the reinforcement elements, the mechanical strength, modulus and toughness of these materials increase significantly (Törmälä 1992). The mechanical properties are also dependent on the basic molecule and the length of the chain (Törmälä 1992).

3. EXPANSION PROPERTIES OF SELF-REINFORCED SELF-EXPANDABLE BIODEGRADABLE STENTS

Viscoelastic behaviour of biodegradable polymers makes possible the memory effect of the material. Injection-moulded polylactide plates possess a viscoelastic shape memory, which can be reduced by annealing treatment (Losken et al 1994). In helical spiral stents the expansion rate depends on the material, the internal arrangement of molecular chains, the initial outer diameter of the spiral, the diameter of the stent wire and the processing conditions. In *in vitro* experiments during expansion the length of the stent has not altered (Losken et al 1994, Välimaa et al 1999). Expansion can be rapid or slow depending on the processing method. Stents are stable in room temperature and expansion occurs at body temperature. The expansion rate of spiral stents may vary from 5 minutes to 2 weeks to achieve the final expansion (Talja et al 1997, Välimaa et al 1998).

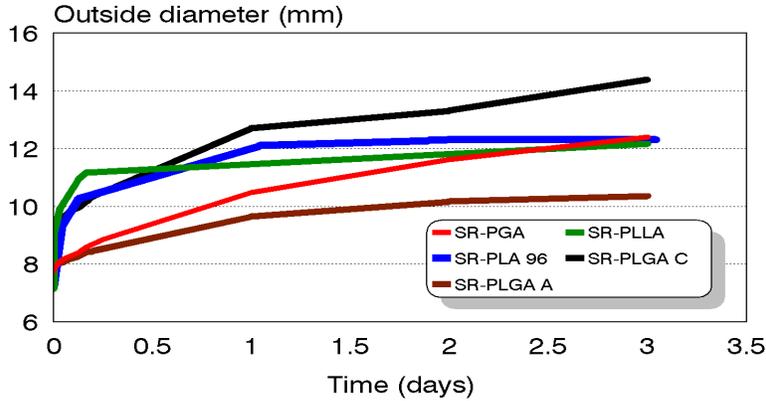


Figure 2. Expansion rates of spiral stents

The degradation rate of the material depends on the moisture content and the temperature prevailing during processing and storage. Processing, sterilization and storage should take therefore place in a dry atmosphere and at as low a temperature as possible. The same factors may have also an effect on the mechanical properties of the stents when taken into use.

The terminology used to refer to the degradation of biodegradable materials has been various: biodegradable, bioabsorbable, absorbable, degradable and resorbable according to the writer. Bioabsorption means degradation and metabolism of the material *in vivo* in tissues first to small particles and subsequently intracellularly to small molecules such as carbon dioxide and water, while in addition energy is liberated. Biodegradation means the morphologic and chemical degradation of material *in vivo*, e.g. in the lumen of tubular organs, and the term degradation represents the general breakdown of the material (Talja et al 1997). The degradation of poly- α -hydroxy materials can be divided into two main stages. First, the process begins in the amorphous regions of the material, the molecular chains between the crystalline and amorphous areas and within the amorphous areas breaking down, which procedure leads to a loss of strength of the material. In the second stage, the crystalline areas begin to degrade (Välilä 1995). The degradation behaviour of each of these polymers can be altered by copolymerization, radiation, thermal treatment and orientation of the material. A helical spiral stent may also be treated in such a way that

the degradation gradually proceeds from one end to the other (Välilmaa et al 1995, Talja et al 1997).

The degradation of PGA and PLA polymers consists mainly in breakage of intramolecular bonds by hydrolysis (Nakamura et al 1989). As a result of this, the process of bioabsorption begins: the material degrades to small particles which are phagocytosed by macrophages. In the case of bioabsorption, macrophages and giant cells initiate the phagocytosis of polylactide and polyglycolide when the particle size is from 10 to 80 μm . Inside the cells, the degradation continues by hydrolysis in lysosomes (Bos 1991, Majola 1992, Bergsma et al 1995). PLA and PGA break first into short molecular chain polymers and then into acid monomers. Poly-L-lactic acid (PLLA) is degraded to L-lactic acid, poly-D-lactic acid (PDLA) to D-lactic acid and PGA to glycolic acid (McNeill and Leiper 1985).

In the intracellular metabolic process SR-PGA is converted into glyoxylate and further into glycine and pyruvate. The rest of the degradation occurs in the citric acid cycle. The end-products are water and carbon dioxide (Frazza and Schmitt 1971).

In the intracellular metabolism process lactate is turned into pyruvate by lactic acid dehydrogenase and further into either acetylcoenzyme-A or oxaloacetate. The further degradation occurs in the citric acid cycle, similarly to that for PGA (Hollinger and Battistone 1986). Several factors govern the rate of hydrolytic scission of polyesters. In tissue culture medium poly-L- (PLLA) lactic acid is less soluble and less susceptible to degradation than is a racemic (PDLA) mixture (Kulkarni et al 1971). As the degree of crystallinity of polymers can affect the rate of water sorption. Therefore the crystalline L form of PLA retards water sorption and degrades more slowly than the less crystalline racemic form (Gilding 1981).

Copolymers of the alpha-polyester class are less crystalline than their constituent homopolymers and consequently degrade more rapidly (Miller et al 1977). The rate at which PLA/PGA copolymers degrade within the body also depends upon the molar ratio

of lactic acid to glycolic acid (Cutright et al 1974). The process of lactic acid hydrolysis is less rapid than that for the glycolic acid units of the copolymer and, therefore, copolymers rich in lactic acid generally degrade more slowly than those rich in glycolic acid (Cutright and Hunsuck 1972).

5. BIOCOMBATIBILITY TESTING

The biological safety evaluation of medical devices is nowadays guided by the revised versions of the documents ISO10993 (International Organization for Standardization) and CEN 30993 (European Committee for Standardization ISO/DIS 10993-Part 1:1995), which were harmonized from numerous international and national standards and guidelines. The selection and evaluation of any new material or device intended for use in humans requires a structured programme of assessment. In the design process, an informed decision weighing the advantages/disadvantages of the various materials and test procedure choices should be made. To ensure that the final product will perform as intended and be safe for human use, the programme of assessment should also include a biological evaluation. The international standard serves as a framework for the planning and execution of safety analysis. Biological evaluation should be planned, carried out and documented by knowledgeable and experienced individuals capable of making informed decisions based on the observed advantages and disadvantages of the various materials and test procedures (Talja 1998).

The biodegradable materials polylactide (PLA, polylactic acid) and polyglycolide (PGA, polyglycolic acid) are both poly-alpha-hydroxy acids and have been widely investigated with an eye to their medical use. There have been numerous published reports on their good biocompatibility. PGA as suture material is well tolerated by the soft tissue, evoking only minimal inflammatory response (Herrmann et al 1970, Heino et al 1999). Devices made from self-reinforced bioabsorbable materials have been used in orthopaedics and plastic surgery for decades and few side-effects have been seen (Cutright and Hunsuck 1972, Vainionpää et al 1989, Majola 1991, Törmälä 1992, Bergsma et al 1995). Degrading implants disintegrate in the body *in vivo* into ever smaller fragments which may cause a nonspecific mild foreign body reaction. When giant cells and macrophages digest polymer particles of size 10-80 μm , the inflammation-activating mediators are secreted and as a result granulation tissue with neutrophilic granulocytes may be seen (Törmälä 1992). Echeverria and Jimenez (1970) showed the biodegradation of macroscopic SR-

PGA implants to proceed by a cellular reaction comparable to the biodegradation reactions to polyglycolide sutures.

Self-reinforced, poly-L-lactide (SR-PLLA) helical spirals stents have shown good biocompatibility with a minimal tissue reaction around the stent in the anterior urethra, whereas spirals of stainless steel have provoked a marked inflammatory reaction (Kemppainen et al 1993). Biodegradable urethral stents have proved in an animal study to possess biocompatibility similar to that of silicone, and better than latex and metallic stents (Isotalo et al 1999).

5.1. Muscle implantation tests

All medical devices should be subjected to specific long-term animal tissue implantation tests in addition to acute toxicity tests. The recommendations for these tests are based on the contact type and intended duration period of the medical device (Biological evaluation of medical devices - Part I 1995).

Selection of the study animal should be based on the life-expectancy of the animal and the duration of the study. The local biological response to implanted materials depends both on the properties of the materials used and on the trauma caused by surgery. Usually after one week's observation high cellular activity is observed, followed by a transitional stage. In muscle implantation a steady state is seen after 9 to 12 weeks (Biological evaluation of medical devices-Part 6 1994).

6. URETHRAL STENTS

Fabian first described the use of an intraurethral stent to relieve infravesical obstruction due to benign prostatic hyperplasia (BPH) (Fabian 1980). The stent was placed in the prostatic urethra to keep it open in benign prostatic enlargement (BPE) patients unfit for surgical procedures. Since then several intraurethral stents have been used for either temporary (removable) or permanent purposes. Among these stents the permanent types incorporate into the tissue (Milroy et al 1988, Nordling et al 1989, Oesterling 1993, Williams et al 1993, Kaplan et al 1993, Montorsi et al 1994, Kletscher and Oesterling 1994, Nissenkorn et al 1996).

6.1. Temporary stents

The temporary stents nowadays commercially available are made of various materials: stainless steel, nickel titanium alloy and biostable polymers. All temporary stents should either be removed or changed every 6 to 36 months (Yachia 1997). All the temporary metal stents are made of coiled wire. Three of the four available designs, the stainless steel Urospiral®, the gold-plated stainless steel Prostakath® and the nickel-titanium Prostacoil® are based on the original Fabian stent. All were developed for the treatment of prostatic obstruction. They have a long segment of body to hold the prostatic urethral lumen open and a bulbar segment to anchor them in place, and a transsphincteric spacer connecting the prostatic and bulbar segments. Memokath® 028 is a single-segment device and upon insertion the entire outer calibre of the stent is 22 F, but when it is flushed with 45°C -50 °C water, a few coils at the level of the prostatic apex expand to 34 F, anchoring the stent in place. The device is removed by flushing the urethra and the stent with cold (10 °C) water. At this temperature, the stent becomes very soft and can be pulled out with endoscopic grasping forceps as a twisted wire (Ellis and Gidlow 1996).

In 1995 Nissenkorn introduced a polyurethane intraurethral catheter with a tubular device with basket dilatation at both ends of the stent, at the bladder neck and at the apex of the prostate (Nissenkorn 1995). The Barnes stent is also a polyurethane device in which the proximal end is similar in design to a urethral catheter, whereas distally a single retaining basket is designed to sit at the verumontanum (Barnes and Yakubu 1998). The Trestle catheter consists of two silicone tubes with a thread connection. The proximal prostatic part has the Foley catheter design and the distal tube is in the bulbous urethra. This type of stent has been used in temporary stenting of the urethra after high-energy transurethral microvave therapy of the prostate (Devonec and Dahlstrand 1998).

Stent	Expansion	Sizes		Material	Indwelling time (months)
		Calibre (Fr)	Length (mm)		
Urospiral® Fabian stent	Non-expanding	21	40-80	Stainless steel	<12
Prostakath®	Non-expanding	21	40-80	Gold-plated stainless steel	<12
Prostacoil®	Self-expanding	24/30	40-80	Nitinol	<36
Memokath® 028	Heat-expandable	22/34	30-70	Nitinol	<36
Barnes® stent	Non-expanding	16	50	Polyurethane	<3
Intraurethral catheter (IUC) Nissencorn stent	Non-expanding	16-18	25-80	Polyurethane	<12

Table 2. Characteristics of temporary nondegrading prostatic stents (Yachia 1998)

Temporary stents have many side-effects, among them migration, encrustation and infection. In a study by Nordling and colleagues (1992), 75 out of 150 prostatic stents had to be removed for various reasons, including proximal (42 stents) or distal (13 stents)

migration; 21 stents had calcifications. Karaoglan and coworkers (1992) have presented results obtained with Urospiral®. In their study of 18 patients the long-term complications included intermittent haematuria in 2 patients (11 %), stent migration in one (6 %) and urinary tract infection in eight (44 %). When correlating Prostacath® and Urospiral® stents the long-term complications in the Prostacath® group included urinary tract infection in 12 %, failure to void in 6 %, urethral stricture in 3 % and stent encrustation in 9 % , while in the Urospiral® group urinary tract infections were 17 %, stent migration 4 %, bleeding 4 % and urethral stricture 4 % (Braf et al 1996). In a Finnish multicenter study presented by Ala-Opas and coworkers (1993), 39 % of the stents had to be removed during the follow-up. Chronic urinary tract infection significantly reduced the functional time of the spiral. In a study by Thomas and coworkers (1993) late effects included stent migration (15 %), recurrent urinary tract infections in 10 % and encrustations in 4 %. Nissencorn and associates (1996) observed no urinary tract infections during two weeks' stenting with an intraurethral catheter after VLAP procedure in a study involving 15 patients with prostatic hyperplasia.

6.2. Permanent stents

The wide spacing between the stent wires allows tissue ingrowth and the stent can thus be permanently embedded in the wall of the tubular structure of the body in which has been placed. Milroy and coworkers (1988) first reported their experience with an endoscopically placed, self-retaining permanent urethral stent for the treatment of bulbar urethral strictures which had recurred after previous treatments. Urolume® has the configuration of a woven, self-expanding tubular mesh made of fine superalloy wire. The stent is placed by a special delivery system which allows direct visualization of the device during placing. Williams and coworkers ((Williams et al 1993) used the same stent in patients with prostatic obstruction. Shaw and coworkers (1990) also used the Urolume® in patients with neurological voiding disorders consequent upon spinal injury. The stent was shown to be stable when expanded. The epithelium is coring the stent entirely during half a year (Oesterling et al 1994). Memotherm® is a heat-expandable stent made of

nitinol and built as a woven tubular mesh (Ricciotti et al 1995). The Gianturco® stent is a modification of Urolume® . It is a self-expanding device made of stainless steel but with larger spacing between the interstices and lesser shortening with increasing diameter (Guazzoni et al 1994). The titanium stent (Titan®) is expanded by inflating a balloon on the insertion catheter (Kirby et al 1992). The stent construction is highly stable without flexibility.

Stent	Expansion	Size		Material	Indwelling time (months)
		Calibre (Fr)	Length (mm)		
Urolume®	Self -expanding	42	20-40	steel superalloy	permanent
Titan®	Balloon- expandable expandable	33	19-58	titanium	permanent
Memo- therm®	Heat- expandable	42	20-80	nitinol	permanent
Gianturco®	Self- expanding	8-12	50	stainless steel	permanent

Table 3. Characteristics of permanent prostatic stents (Yachia 1998)

The problems with permanent stents are similar to those encountered with temporary stents. In a study of 47 patients the stent was removed in 14 out of the 36 patients followed up for two years. The main indications for removal were stent migration or epithelial hyperplasia obstructing the stent lumen (Bajoria et al 1995). The urinary tract infection rate at 12 months' follow-up was 16 % and stent encrustation 7 % in the follow-up study of 96 patients with fitted Urolume® (Williams et al 1993). The risk of encrustation is increased if the stent fails to be covered by the epithelium (Milroy and Chapple 1993).

6.3. Biodegradable stents

The anterior urethra was the first anatomical location chosen for the use of biodegradable spiral stents in urology. A bioabsorbable SR-PLLA stent was first introduced in an experimental study by Kemppainen and coworkers (1993). The first biodegradable stent used in humans was a SR-PGA spiral stent. The clinical results in preventing postoperative urinary retention were encouraging after visual laser ablation of the prostate (VLAP) (Talja et al 1995, Petas et al 1997a).

The configuration of the spiral stent was reminiscent of the Fabian: it has an outer diameter of ~8 mm (24F) and a prostatic portion varies from 45 mm to 75 in length. A transsphinctering single stent wire connected the prostatic body to the distal bulbous portion of new spiral rings (Figure 1). At body temperature the outer diameter of the spiral stent increased more than 60 % in consequence of the tendency of the spiral to straighten.

The spiral was inserted by pushing it with the tip of the cystoscope into the prostatic urethra over a ureteral catheter as guidewire. When SR-PGA spiral stents were used after VLAP therapy, voiding resumed within two days subsequent to therapy in 86 % of cases (42/49 patients) compared to 34 % (8/23 patients) if no prostatic stent was used to drain the bladder. In the indwelling catheter group voiding commenced during the two days following a catheterization of six days in 82 % (18/22 patients). The total urinary tract infection (UTI) rate was lower in the spiral stent group (26 %) than in the suprapubic (35 %) or indwelling catheter groups (36 %). The DAN-PSS-1 (Hald et al 1991, Hansen et al 1996) -weighted symptoms and peak flow rates in the bioabsorbable spiral stent group were comparable to those in the other two groups (Petas et al 1997a). Some patients noted a deterioration in urinary flow three to four weeks after the operation, which corresponds to the degradation time of SR-PGA spiral stents. The flow recovered within a few weeks. Judging from these observations it was evident that the degradation time of SR-PGA was

too short for the total resolution of prostatic oedema after VLAP therapy (Talja et al 1995, Petas et al 1997b, Petas et al 2000).

SR-PGA spiral stents have also been used in combination with high-energy transurethral microwave thermotherapy (TUMT) to prevent postoperative urinary retention (Dahlstrand et al 1997, Devonec and Dahlstrand 1998). Instead of requiring an indwelling catheter after TUMT for 14.1 ± 3 days in patients with a large prostatic volume (75.1 ± 21 cm), all patients fitted with a prostatic SR-PGA spiral stent were able to void immediately after therapy. The peak flow in these patients had increased from 6.1 ± 2.8 to 13.9 ± 3 ml/s when measured after 3 months. In the catheterized group, the peak flow rate was similar (13.3 ± 2.1 ml/s).

In 45 patients undergoing VLAP due to BPE, voiding resumed on the first or second day after treatment in 18 out of 22 patients (82 %) fitted with the SR-PLA 96/4 stent immediately after laser therapy and in 8 out of 23 (35 %) without the prostatic stent (Petas et al 1997a). Improvements in patient weighted symptom score, mean maximum flow and urine residual volume were parallel and significant in both groups at the 6-months' follow-up. The mean degradation time of the SR-PLA stent in clinical use was 6 months (Petas et al 1997a), which is unnecessarily long for most indications. The *in vitro* biodegradation of SR-PLA 96/4 spiral stents was measured to be the same, 30 weeks (Välimaa and Törmälä 1998).

7. ENCRUSTATION OF BIOMATERIALS

The process by which crystalloids and colloids adhere to biodegradable and non-biodegradable biomaterial surfaces is referred to as encrustation (Choong and Whitfield 2000). Device-related urinary tract infections and encrustation are common complications, causing significant morbidity, and are the major limiting factors in long-term use of biomaterials within the urinary tract (Denstedt et al 1998). Encrustation rates up to 58-76 % have been reported with ureteric stents indwelling for more than 12 weeks (El-Faqih et al 1991, Keane et al 1994). Encrustations increase with the duration of stenting - only 6 % of stents were encrusted at six weeks (El-Faqih et al 1991). The encrustation process is complex, initially involving urinary protein adsorption onto the device surface, followed by conditioning film and biofilm formation. Both biofilm formation and encrustation increased with the duration of stenting (Keane et al 1994). The mechanism of encrustation and stone formation in the presence of urease-forming organisms has been documented both *in vivo* and *in vitro* (Griffith et al 1976).

In assessing the protein content within the conditioning film formed *in vivo* on ureteral stents by electrophoresis, were differences in protein profiles identified between nonencrusted and encrusted stents (Santin et al 1999). Urease-producing bacteria adhere to the biofilm, multiply and cause an elevation in urinary pH. Scanning electron microscopy (SEM) has confirmed bacterial presence within biofilms on encrusted catheters (Reid et al 1995) and localized production of urease from within a biofilm has been experimentally demonstrated (Wilksch et al 1983). Many biofilms are defined by four components: first, a linking film attaching to the surface of tissues or materials; second, a base film containing the surface of tissues or materials; third, a base film containing compact organisms and, fourth, a surface film from which planktonic organisms may spread to other sites (Reid 1999). The exact mechanism of encrustation in sterile urine is not completely understood but appears to depend on both urinary constituents and the properties of the biomaterial. Sterile encrustations are often composed of calcium oxalate (Reid et al 1995). *In vitro*

studies in which sterile conditioning films formed on ureteral stents exposed to artificial urine resulted in intraluminal encrustation (Santin et al 1999).

8. PROSTATE TREATMENTS INDUCING OBSTRUCTING OEDEMA

8.1. Transurethral resection of prostate (TURP)

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate due to excessive growth of the glandular and stromal elements and constitutes the most frequent urologic problem in ageing men, affecting 40-70 % of men aged 60 to 70 years, as judged by histopathological and clinical criteria (Berry 1984, Garraway 1991). Nearly 80 % of men will develop BPH, and nearly 30 % will undergo surgery for their condition (Glynn et al 1985).

The aetiology of BPH is multifactorial, advanced age and the presence of functioning testes being the two best-established factors required for the development of the condition (Guess 1995). The natural history of BPH varies considerably. Symptoms BPH are variations but usually increase with age (Jacobsen et al 1997). They may be divided into two groups, emptying (obstructing) and storage (irritating) symptoms (Schulman 2001). Shatzl and colleagues (2001) studied the prevalence of lower urinary tract symptoms (LUTS) and found that a mean increase of 43.7 % from the youngest (20-39 years) to the oldest (>70 years) age group. In a population-based Minnesota study of 2115 men the cumulative incidence of acute urinary retention (AUR) increased with age, a 60-year-old man having a 23 % probability of experiencing retention if he was to reach the age of 80 (Jacobsen et al 1997). AUR is also one of the main indications for surgery, constituting the presenting feature in 25-30 % of transurethral resections of the prostate (TURP) (Schulman 2001). The risk of AUR appears to be independently modified by age, by more urinary symptoms and by a reduced peak urinary flow rate. It is also influenced by the presence of large prostate (Jacobsen et al 1997).

TURP is the standard surgical treatment for BPH and significantly alleviates the patient's symptoms and voiding dysfunction. Perioperative complications have been reported in 7 to 14 % and postoperative complications in 17 to 18 % of patients undergoing TURP (Mebust et al 1989, Doll et al 1992). Up to 25 % may not show satisfactory clinical improvement from the operation (Oesterling 1995). The annual reoperation rate is estimated to be about 1 % to 2 % (Roos et al 1989, Wasson et al 1995). The mortality rate in transurethral prostatectomy has been reduced from 2.5 to 0.2 % during the last 27 years (Mebust et al 2002).

8.1.1. Interstitial laser coagulation of the prostate (ILCP)

Interstitial laser coagulation of the prostate is one of the thermal treatment approaches. The objective of ILCP for treatment of BPH is to achieve volume reduction and improvement in clinical symptomatology. This is accomplished by inducing a coagulative necrosis within the prostate rather than on its urethral surface like as in VLAP (Muschter et al 1996). As energy source a solid-state, diode laser with 830 nm wavelength is used. The energy is transmitted through a flexible 600 μm laser fibre (diameter 0.98 mm). At the distal end of the fibre is a 1-cm cylindrical diffuser area (diameter 980 nm) emitting energy in all directions. ILCP is performed with a standard cystoscope. Under direct visualization the laser fibre is introduced directly into the prostate gland and low-power thermal energy is delivered to heat and destroy prostatic tissue. The fibre can be introduced into side lobes and with care into the median lobe of the prostate. The number of sites for the application of energy is determined individually for each patient, depending on the size and configuration of the gland. Muschter and associates (1996) studied the clinical efficacy of ILCP using diode laser energy in a prospective, nonrandomized multicenter trial. The results reported are excellent, with a significant decrease in symptoms and a significant increase in Qmax (+132 %). Similar results have also been reported by groups under Arai (1996) and Horninger (1997).

The significant difference between ILCP and standard TURP is the lack of immediate relief of prostatic-induced obstruction, which is also common in other laser treatments for BPE. In ILCP the shrinkage of the prostate takes place within 6-8 weeks after treatment, so that no significant improvement occurs until after this time and the incidence of postoperative acute urinary retention is unacceptably high (Muschter et al 1993 and 1996). The need for catheterization following ILCP has been of approximately the same magnitude (40-45 %) as after visual laser ablation of the prostate, the majority of cases less than one week in (Muschter and Hofstetter 1995, Daehlin et al 1997, De laRosette et al 1997).

8.1.2 Other treatments

Postoperative prostatic oedema also complicates other prostatic procedures such as transurethral needle ablation of the prostate (TUNA), transurethral microwave therapy (TUMT), transrectal high-intensity focused ultrasound (HIFU) and ethanol injection (Issa 1996, Campo et al 1997, Viridi et al 1997, Nakamura et al 1997, Mulligan et al 1997, Ramsey et al 1997). The TUNA device delivers low-level radiofrequency (RF) energy to the prostate through needles inserted transurethrally. An intraprostatic temperature up to 80-200 °C can be achieved (Issa 1996). TUNA is performed as an outpatient procedure with the patient under local periprostatic anaesthesia, although intravenous sedation is frequently needed. Postoperative urinary retention lasting for a mean 1-3 days is seen in approximately 30 % of patients and within one week, 90-95 % of patients are catheter-free (Issa 1996, Campo et al 1997, Viridi et al 1997). Transient, self-limiting haematuria is experienced by most patients but blood transfusions are not needed. Irritative voiding symptoms, lasting up to 4-6 weeks, are frequently present. Sexual function and continence status are not affected (Issa 1996, Campo et al 1997, Viridi et al 1997). Zlotta and colleagues evaluated 188 patients with symptomatic BPH treated with TUNA and 23.3 % required additional treatment at 5 years follow-up (Zlotta et al 2003).

Transurethral microwave thermotherapy (TUMT) is another new mini-invasive technique for the treatment of BPH. Treatment requires intravenous sedative analgesia in some patients. Techniques range from low-energy TUMT, where a 45-60 °C intraprostatic temperature is achieved, to high-energy TUMT, with a 60-80 °C temperature (Djavan et al 1999). The enhanced efficacy of high-energy TUMT is associated with an increase in postoperative morbidity (de la Rosette et al 1997, D'Ancona et al 1997, Ramsey et al 1997). The most bothersome complication is prolonged retention averaging 10-14 days with a frequency of 6 – 11 % in those undergoing high energy TUMT. In these cases the mean duration of catheter drainage has been 17.5 days (Ramsey et al 1997). Long-term data is rare. A total of 1092 patients (average age 67 years) were treated with lower-energy TUMT and the absolute instrumental retreatment rate was 26 % after 5 years (Francisca et al 1999).

The use of HIFU in the treatment of BPH was first described in 1992. The efficacy of the approach (achieved intraprostatic temperature 100°C) is in the range of high-energy TUMT and TUNA. A transrectal HIFU operation requires general anesthesia. The most prominent side effect is prolonged urinary retention, lasting for 3-6 days in up to 40 % of patients (Madersbacher et al 1996, Nakamura et al 1997, Mulligan et al 1997, Sullivan et al 1997). In a study of Schatzl et colleagues compare the efficacy of TURP versus four less invasive treatment options(TUVP,VLAP,TUNA,HIFU) during a 2-year follow-up and in up to a quarter of the patients a secondary TURP was performed (Schatzl et al 2000).

Direct injection of dehydrated ethanol is another new mode of minimally invasive treatment for BPH. According to preliminary reports the risk for postoperative urinary retention seems to be increased in comparison with other mini-invasive therapy methods. Goya and coworkers (1999) evaluated the efficacy of this technique in 10 patients with BPH. Postoperative urinary retention occurred in all patients and the urethral catheter could be removed after 3 to 22 days (mean duration 8.8). Voiding improved gradually from weeks 2 to 4 after ethanol injection therapy and significantly after 3 months compared to preoperative data. Ditrollo and coworkers (2002) treated 15 patients with documented outlet obstruction secondary to BPH using the InjecTx® endoscopic device.

The mean size of the prostate was 48 ml (range 22-75 ml). The average ethanol injection dose per injection site was 3.8 ml (range 2 to 6) and average total alcohol dose 13.1 ml (range 8 to 22). Postoperatively catheter drainage was applied for an average of 3.6 days (range 3 to 10) (Ditrolio et al 2002).

8.2. Prostate cancer

Adenocarcinoma of the prostate is the most common cancer to occur in men and remains the second leading cause of death from cancer in men in the Western world (Wingo et al 1998). Treatment options for prostate cancer have involved watchful waiting, radical prostatectomy, external beam radiation therapy, interstitial radiation therapy (brachytherapy) , and endocrine and cytostatic therapy.

8.2.1. Brachytherapy

Ultrasound-guided prostate brachytherapy with either iodine 125 (I-125) or palladium 103 (Pd-103) intraprostatic seed implantation has recently come to be viewed as an alternative treatment for many prostate cancer patients with intraprostatic involvement. Brachytherapy can be delivered to the prostate either with permanent seed implants or with removable implants, which are often delivered at a high dose rate with iridium wire. Contra-indications for permanent seed implants are a life expectancy of less than 5 years, the presence of metastatic disease, recent TURP with persisting large prostatic defect, and bleeding disorders. In addition, patients with a prostate gland greater than 50 ml have a high probability of pubic arch interference (Ash et al 2000). After brachytherapy approximately 15 % of patients may develop acute urinary retention either immediately or within a few days following implantation (Brosman et al 1991). However, by excluding patients with significant bladder outlet obstruction the retention rate can be reduced. In more recent studies urinary retention after brachytherapy has been less than 10 % (Terk et al 1998). Urinary retention is usually due to post-implant oedema and is usually managed by urethral catheterization. In the majority of patients micturation resumes within 2 weeks as the oedema resolves (Ash et al 2000). Practically all patients develop urethritis of variable intensity and duration. Symptoms are often helped by alpha-blockers and non-

steroidal anti-inflammatory drugs. Proctitis may also occur in a few patients and can be alleviated by steroid enemas. The risk of infection is low but many centres routinely use antibiotics after implantation (Prestidge et al 1998). TURP should be avoided in view of the high risk of postoperative incontinence (Hu and Wallner 1997).

AIMS OF THE STUDY

The challenge for the urological community is to evaluate which type of stent is the best suited for a specific application in a specific patient. Clinically a need has been perceived for a biomaterial stent which degrades in two to three months, and to this end a self-reinforced polylactic-glycolic acid (SR-PLGA) helical spiral stent has been developed. In the present study the properties of this new stent were investigated aiming especially to find answers to the following questions:

1. What are the viscoelastic memory and expansion properties of the SR-PLGA 80/20 spiral prostatic stent? (I, IV)
2. What are the encrustation and mechanical properties of the PLGA 80/20 material *in vitro* and *in vivo*? (II, III)
3. What are the intramuscular and urethral *in situ* biocompatibility properties of the SR-PLGA 80/20 stent material? (III)
4. What is the feasibility, safety and efficacy of the SR-PLGA 80/20 prostatic spiral stent when used to prevent postoperative urinary retention after procedures inducing prostatic oedema? (V)

MATERIALS

1.1. Biodegradable materials

The biodegradable polymer PLGA 80L/20G is a copolymer of lactic and glycolic acid (the lactic /glycolic ratio being 80/20). The raw material was obtained from Purac Biochem b.v (Gorinchem, Netherlands).

The self-reinforcing (SR) of the stent wires was accomplished by solid-state drawing. The self-reinforcing and winding of the stents was carried out in Bionx Implants Ltd (Tampere, Finland). The PLGA polymer was amorphous as received and crystallization of the material was effected in a WTB Binder vacuum oven 16 hours at +110 °C temperature. In mechanical and compression testing (II) the PLGA 80/20 polymer was extruded into cylindrical rods which were further processed into self-reinforced (SR) wire by solid-state die-drawing. Wires were wound over a stainless steel mould to the shape of the Fabian prostatic stent. The outer diameter of the device was 8 mm and the prostatic section 45, 55, 65 or 75 mm long (IV,V). The PLGA 80/20 material was sterilized by gamma irradiation (dose 2.5 MRad). The outside diameters the stents used in the animal study (III) were 5 mm (± 0.2) and the prostatic part of the stents was 40 mm in length. In the animal muscle implantation study (III) the rods were 1.1 mm in diameter and 10 mm long cut from SR-PLGA 80/20 wire.

In the study concerning the viscoelasticity and self-expansion of the spiral stents (I) the polyglycotide (PGA), poly-L-lactide (PLLA) and poly-L, D-lactide (PLA, L/D ratio 96/4) materials were also obtained from Purac Biochem b.v. and the self-reinforcing (SR) was done by solid-state drawing in Bionx Implants Ltd (Tampere, Finland) like the PLGA 80/20 material used in this study. In study (I) the diameters of the wires were 1.15 ± 0.05 mm. Stents were wounded over a stainless steel mould. After winding the stents were

annealed in different temperatures in a Memmert ULP500 (Germany) convection oven. The initial outside diameter of the stents was 7.4 ± 0.7 mm (Ch 23) and 6.4 ± 0.7 mm (Ch 21).

For encrustation studies (II) a 7-mm-long segment of the test material for the SR-PLGA 80/20 stents was incubated *in vitro* in sterile artificial urine. For compression strength studies (II) 20-mm-long pieces of manufactured SR-PLGA 80/20 spiral stent wire were incubated in sterile artificial urine for 12 weeks and measurements made by compressing the specimens between two parallel planes at 2, 4, 6, 8 and 12 weeks. Analyses were made in triplicate. The SR-PLGA 80/20 spiral stent segments used in the compression strength analysis (II) were 20 mm in length and 10 mm in diameter.

1.2. Control materials

In the muscle implantation tests (III) rods made from a pure silicone catheter were used as negative controls and as positive controls similar rods from a brand of latex catheter (Silkolatex®, Willy Rusch AG, Germany) previously discovered to be toxic (Ruutu et al 1985, Talja et al 1985) were used in the first 10 rabbits; for the remainder the positive control rods were made of PVC organotin positive control material (ISO10993-6, Sims Portex Ltd, UK).

In the urethral *in situ* implantation test (III) stents made from stainless steel wire used in the tension band system in orthopedics were used as controls (Dentaurum® 0.50 mm, Germany). The steel stents were manufactured by Bionx Implants Ltd. (Tampere, Finland), the configuration being identical to that of biodegradable stents.

For encrustation studies (artificial urine) (II) 7-mm-long segments of Prostakath® and Memokath® metallic stents were used as controls. Prostakath® (Doctors and Engineers Inc. Copenhagen, Denmark) is a gold-plated spiral based on the original Fabian stent developed for prostatic obstructions (Nordling et al 1989). Memokath® 028 (Engineers &

Doctors A/S Ltd, Kvistgård, Denmark) is a single-segment device with a coil of nickel-titanium thread with an outer diameter of 22 Ch (Ellis and Gidlow 1996).

1.3. Patients

1.3.1. Expansion and biodegradation of the SR-PLGA stent (IV)

Thirty-nine men (aged 52-84 years) evincing lower urinary tract symptoms due to BPE underwent interstitial laser coagulation of the prostate (ILCP) and an SR-PLGA 80/20 stent was inserted in the prostatic urethra at the end of the operation.

1.3.2. The SR-PLGA stent in ILCP (V)

Fifty patients (aged 52-85 yeras) from Tampere University Hospital and Päijät-Häme Central Hospital with obstructive symptomatic BPE were allocated to the pilot study from a waiting list for prostatic surgery. The patients underwent ILCP and an SR-PLGA spiral stent was inserted.

2. METHODS

2.1. Viscoelastic memory and stent expansion (I)

The initial outside diameter of the stents was 7.4 ± 0.7 mm (23Ch) and 6.4 ± 0.7 mm (21Ch). All analyses were made in triplicate. The stent samples were immersed in Na_2HPO_4 - KH_2PO_4 buffer solutions at pH 6.1 and 0.1 M at $+37^\circ\text{C}$. The outside diameter of each three parallel stent sample was measured periodically from three points of the spiral. The measured expansion rate was examined by regression analysis.

2.2. Encrustation, biodegradation and compression strength properties (II)

In the encrustation analysis 7-mm long segments, 3 samples for each tested material of SR-PLGA 80/20, Prostakath® and Memokath® stents were used. The test material was incubated in sterile artificial urine for 4 and 8 weeks and SR-PLGA 80/20 also for 12 weeks. After incubation the stents were rinsed with saline and fixed in 2 % glutaraldehyde. The specimens were dehydrated in an ethanol cascade, dried in a critical-point dryer and coated with gold in sputter. Scanning electron microscope (SEM) analysis was made at a magnification of 100x from 5 randomly selected areas per each sample. Analyses were made using the computerized Analysis 2.1 program, (Soft-imaging System, GmbH, Munster, Germany) and the Scion Image Beta 3b Acquisition and Analysis Software system (Scion Corporation, USA). The results were presented as a mean percentage of whole analysed area covered by encrustation in each tested material.

In the strength studies the tested samples of SR-PLGA 80/20 stents were 10 mm in diameter and 20 in length and three samples were tested in parallel at each point. The test was performed with a MTS 2/M Universal Compression Testing Machine (MTS Systems France, Ivry sur Seine, France) at room temperature with a testing speed of 10 mm/min. The tests were made between two parallel planes by the compression tool presented in Figure XX. The length of the compression plane was 10 mm. The stent was compressed until the spiral buckled or broke down. The maximum force of compression was measured.



Figure 3. PLGA 80/20 prostatic stent

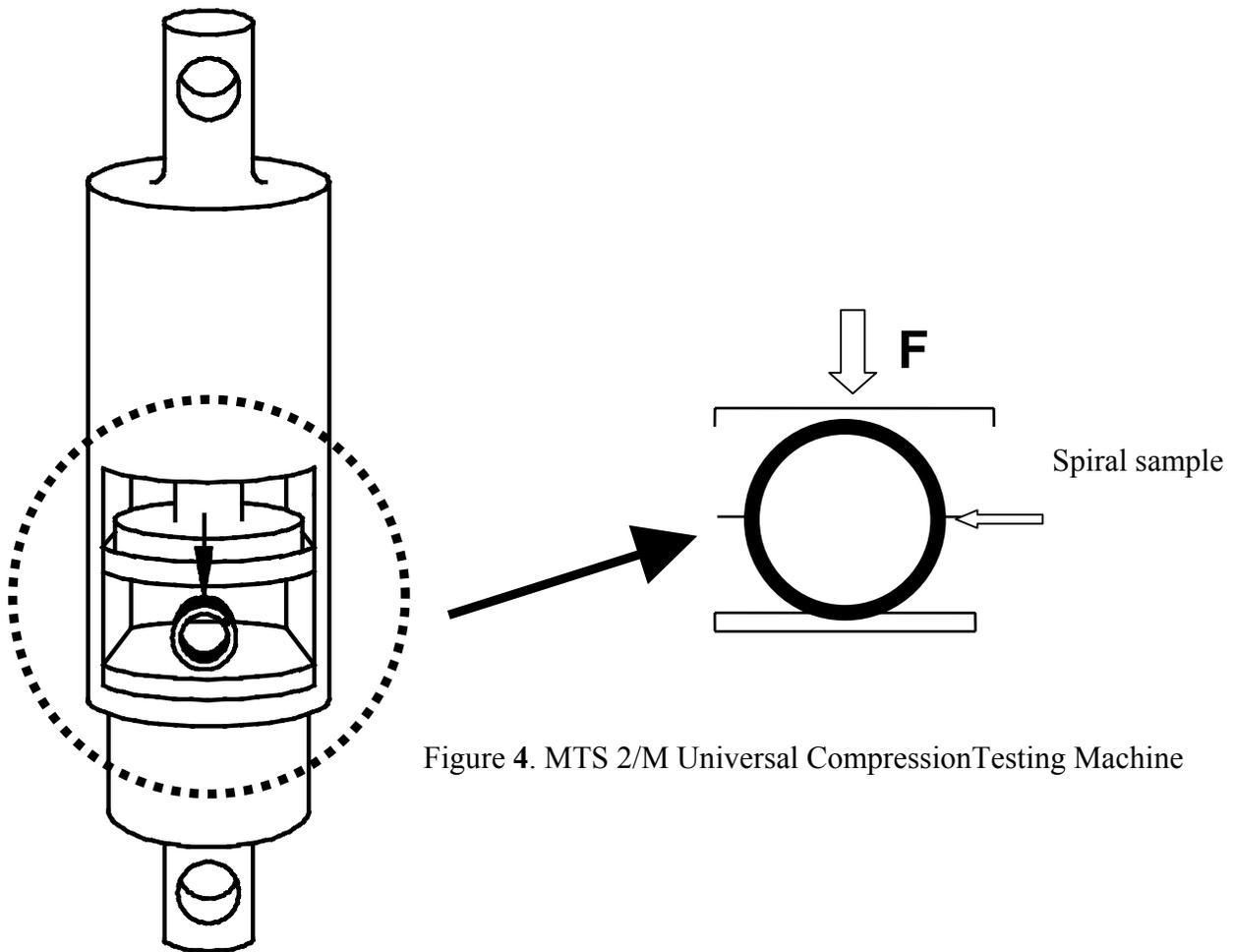


Figure 4. MTS 2/M Universal Compression Testing Machine

2.3. Biocompatibility testing (III)

2.3.1. Animal studies

These studies were carried out following the recommendations and guidelines in the European Convention for Protection of Vertebrate Animals Used for Experimental and Scientific Purposes (CEN 9330:2). A total of 29 male rabbits (New Zealand White) of median size 4.0 kg (range 3.0-5.0 kg) were used as experimental animals. Anaesthesia was achieved with intramuscular medetomidin (Domitor®) 0.3 ml/kg and ketamin hydrochloride (Ketalar®) 0.3 ml/kg i.m. Enrofloxacin (Baytril®) 5 mg/kg i.m. was given as prophylactic antibiotic, with buprenorphine (Temgesic®) 0.05 mg/kg s.c. as analgetic drug for the first postoperative days. The rabbits were allowed to breathe freely, no relaxants were given and intubation was not needed. At the end of the study the animals were sacrificed by administration of pentobarbital (Mebunat R®) 1 mg/kg intravenously.

2.3.2. Surgical procedure

In the muscle implantation test procedure a dorsal midline skin incision was made and the implants were placed on both sides of the dorsal muscles, 8 implants/rabbit (III). The implants were placed under visual control through a 2.0 mm i.v. cannula. The implantation sites were marked in the fascia with 4-0 Prolene® sutures. In the prostatic spiral stent implantation test 29 male rabbits were used. The urethra was first dilated with a Hegar probe to a diameter of 9-10 mm. After dilatation the stent was inserted into the prostatic urethra under direct visual control, pushing with the tip of a paediatric cystoscope (Ch 14). In the first seven animals the stents were not fixed and most of them were voided out. The rest of the stents were fixed through the distal ring of the stent into the urethral wall by two non-resorbable 3-0 sutures (Prolene®) to prevent postoperative gliding.

2.3.3. Microscopic analysis

In the muscular implantation test the test specimens with surrounding muscular tissue were excised. In the urethral *in situ* test the whole proximal urethra with the distal part of the urinary bladder was excised. All samples were fixed in 10 % phosphate-buffered formalin. After fixation the sections were stained with haematoxylin and eosin. The biological response parameters assessed and recorded included acute inflammatory changes, necrobiosis, chronic inflammatory changes, foreign body reactions, fibrosis and eosinophilic reactions. Tissue reactions to the implants were scored semiquantitatively according to the following criteria: - no reaction, + mild reaction, ++ moderate reaction and +++ marked reaction.

2.4. Clinical trials

2.4.1. ILCP and insertion of the SR-PLGA spiral stent.

The ILCP therapy was performed under spinal anesthesia. A single dose of ciprofloxacin (500 mg) 2 hours preoperatively was used for antibiotic prophylaxis, followed by oral sulfa-trimethoprim or nitrofurantoin for 2 weeks. A suprapubic catheter was inserted in all patients. The interstitial laser fibre was inserted repeatedly into the prostatic tissue through a cystoscope under direct vision. The number of fibre placements depended on the size and configuration of the gland. Laser power setting was according to the power-formatting programme stepwise from 10W to 5W Nd: YAG by the ILC machine (Ethicon Endo-Surgery, Inc., Munster-Hiltrup, Germany). A biodegradable self-reinforced SR-PLGA 80/20 spiral stent was inserted into the prostatic urethra after ILCP. The stent was at least 5 mm longer than the prostatic urethra in order to reach into the urinary bladder. The suprapubic catheter was removed after commencement of voiding started.

2.4.2. Expansion and biodegradation of the SR- PLGA stent (IV)

The SR-PLGA 80/20 stent lumen diameter was 4.5 mm. The location and diameter of the lumen and state of degradation of the stent were studied using transrectal ultrasound at 1 month and 2, 4 and 6 months afterwards. At 6 months the patient underwent cystoscopy.

2.4.3 The SR-PLGA stent in ILCP (V)

The study patients underwent ILCP and an SR-PLGA 80/20 spiral stent was inserted. The follow-up assessment consisted of uroflowmetry, ultrasonographic estimation of post-voiding residual urine, transrectal ultrasound, urine culture and a patient-weighted symptom score with bother score (the combined DAN-PSS-1). The assessments were made preoperatively and at 1, 2, 4 and 6 months after ILCP. In addition, the patients underwent urethroscopy at 6 months.

RESULTS

1. *IN VITRO* TESTING

1.1. Viscoelastic and mechanical properties (I)

The expansion of the SR-PLGA80/20 prostatic stent was as rapid as that of the SR-PLA copolymer prostatic stent in the first hours. After one day the SR-PLGA80/20 stent expanded more rapidly than the SR-PLA copolymer stent. The final expansion of SR-PLGA80/20 was 100 % in eight days. The SR-PLLA stent expanded more rapidly than the SR-PLA copolymer stent due to the higher specific rigidity of the former. The expansion rates of the SR-PLA, SR-PLA and SR-PLGA 80/20 stents were greatest during the first few hours, slowing down thereafter and ceasing at a certain level. This level depended on the material, draw ratio, the initial diameter of the spiral, the diameter of the wire and annealing temperature. Regression analysis proved that the expansion behaviour of self-reinforced bioabsorbable stents can be estimated by the logarithmic equation given below. Based on these results annealing temperature and expansion time were directly proportional to the expansion rate of the stent.

$$D_0 = A * \ln(\text{time}) + B * (\text{temperature}) + C$$

where

D_0 = outside diameter of the stent

A and B = coefficients depending on the outside diameter of the stent

C = constant depending on the outside diameter of the stent

1.2. Encrustation and biodegradation and compression strength properties (II)

Areas covered by encrustation at 4 weeks were in Memokath® 8.01 %, in Prostakath® 1.49 % and in SR-PLGA 80/20 0.00 %, at 8 weeks in Memokath® 28.4 %, in Prostakath® 4.1 % and in SR-PLGA 0.12 % and at 12 weeks in SR-PLGA 0.12 %.

In compression strength studies the compression strength of SR-PLGA 80/20 started to decrease after six weeks and after 8 weeks was 35 % of the initial. At 12 weeks it had fallen to 26 N, i. e. 14 % of the initial value. The stents did not shorten during expansion and the length remained constant. The distance between the spiral rings increased as the spiral wire straightened.

2. BIOCOMPATIBILITY TESTING (III)

In the rabbit muscle implantation test the tissue reaction to the SR-PLGA stent resembled that of the negative control silicone. Less than moderate chronic inflammatory changes gradually subsided after two weeks.

All animals voided normally after stent insertion. No SR-PLGA material had invaded the urethral wall macroscopically or microscopically. No calcification was seen on SR-PLGA stents or urinary stones. SR-PLGA 80/20 stents were soft, partly fragmented and easily disintegrated when touched at 2 months, and at 3 months were almost totally degraded. After 3 months two out of six metal stents were deeply implanted in the urethral mucosa. Foreign materials and foreign material reaction seen in the tissue and the reaction to these began to disappear after one month, and at three months were totally absent. No long-term fibrous or toxic effects were observed after bioabsorption of the stent material.

3. CLINICAL STUDIES

3.1. Expansion and biodegradation (IV)

All except one patient started to void on the first postoperative day and after the relocation of the one too proximally located stent the patient in question also started to void. The length of the stent was extended on the average 10 mm (range 7-12) at 1 month. The mean diameter of the stent lumen increased from 4.5 mm to 7.4 mm (range 6.2-8.2) at 1 month and 7.2 mm (range 6.2-7.5) at 2 months. At two months many of the stents were already broken into large fragments and in 3 cases no stents could be seen in the prostatic urethra. Two of these were later found in the bladder. At 4 months small pieces of stents were seen in the prostatic urethra in one of 9 patients. At 6 months no further fragments were found in the prostatic urethra in ultrasound or cystoscopy. In the bladder pieces of spirals could easily be broken into small fragments with forceps and irrigated out through a cystoscope. No calcification of stents or bladder stones was discovered.

3.2. ILCP combined with PLGA 80/20 biodegradable stent in the treatment of benign prostatic hyperplasia (V)

All except three patients started to void on the first postoperatively day. Twenty-five relost voiding to be normal and 15 slow, and 7 patients could void only drops. All of these patients could, however, empty the bladder satisfactorily. In two cases the stent had moved proximally and had to be relocated, after which voiding succeeded. One patient started to void spontaneously after one week. The mean maximum and average flow rates increased while DAN-PSS-1 and post-voiding residual urine decreased, all statistically significantly. At 2 months the stent was still present intact in the urethra in all except 3 patients; at 4 months it was degraded into small fragments and at 6 months completely eliminated. The only exceptions were three cases with an uncalcified piece of the stent in

the bladder. Some half of the patients had irritative symptoms caused at least partly by the ILCP itself, while five (10 %) had asymptomatic urinary infection postoperatively. No strictures or urinary stones were seen during the follow-up.

DISCUSSION

1. VISCOELASTIC MEMORY AND SELF-EXPANSION PROPERTIES

Two basic types of self-expanding stents, both mesh design and helical spirals are nowadays available. The expansion property of these devices is based on mechanical deformation by axial forces or by twisting the stent wire before insertion and releasing the forces *in situ* (Loshakove and Azhari 1997). We demonstrated that the viscoelastic memory of the SR biodegradable materials makes expansion possible both *in vitro* and *in vivo*. Previous *in vitro* studies have shown that the expansion rate and speed depend on the material, the internal arrangement of molecular chains, the diameter of the stent wire, the initial outer diameter of the spiral and the processing conditions (Jebwab and Clerc 1993). We found that the expansion rate can be estimated by a logarithmic equation if processing parameters are constant. The possibility of deciding the speed and rate of expansion is of great clinical importance, since there are different kinds of needs in different indications. The expansion of the stent to its final diameter may range from 5 minutes to 2 weeks (Talja et al 1997, Välimaa et al 1998). In most urological indications rapid expansion would be preferable. Although the expansion of the SR-PLGA 80/20 stent continued for three days it was greatest during the first few minutes and hours, which was sufficient to lock the stent in place rapidly after insertion and effectively prevented migration. The SR-PLGA 80/20 spiral stents are stable at room temperature; expansion occurs at body temperature. They can thus be stored in room temperature and expansion does not occur until inserted in the patient. The tested product has ideal expansion properties compared with the previous self-reinforced SR-PLLA double helical spiral urethral stent, which expanded even too fast in a few minutes in body temperature and had to be stored in -20°C (Isotalo et al 1998).

Although in *in vitro* experiments at body temperature the expansion rate of the SR-PLGA 80/20 spiral stent was 100 %, here in the prostatic urethra, the expansion rate was only around 60 % in three days. The reason for this was probably the resistance caused by the prostatic lobes in patients with benign prostatic enlargement. The expansion rate did, however, suffice to ensure voiding in cases of oedema-induced bladder outlet obstruction.

Another finding of great clinical importance was that in both the *in vitro* and clinical tests the length of the SR-PLGA spiral stent did not shorten with expansion, which makes it possible to select exactly the right length of stent for each patient. An over-long stent can cause bladder irritation or incontinence, when located in the sphincter area. Shortening up to 50 % with expansion is a major problem with net-sleeved metallic stents (Oesterling et al 1994, Guazzoni et al 1994, Entwisle et al 1996). It is concluded that expansion properties of the SR-PLGA spiral stent seems to be optimal for most urological indications.

2. ENCRUSTATION AND STONE FORMATION

In the artificial urine experiment, the resistance to encrustation of the new SR-PLGA 80/20 material was clearly superior to that of the metallic stents and the results were in accord with previous experiments where biodegradable materials have been tested. Kemppainen and associates (1993 in an animal study) showed only few encrustations on self-reinforced polylactic acid (SR-PLLA) stents compared to stainless steel stents in the anterior urethra of a rabbit. Petas and colleagues (1997c) found no encrustations on SR-PGA or SR-PLA stents after two weeks' incubation in artificial urine, but some appeared found on gold-plated steel wire. The absence of encrustation on biodegradable material in this and in the previous series may be explained by the sloughing of the surface of a biodegradable stent in consequence of the continuous hydrolyzation. On the other hand, coating of a biodegradable stent with a biodegradable caprolactone-L-lactide did not prevent encrustation (Multanen et al 2002). This suggests that it is not continuous hydrolyzation alone, which protects from encrustation; but the properties of the biodegradable material itself are also of importance.

Although encrustation was most substantial on the nickel-titanium prostatic stent (Memokath®), the gold-plated stainless steel stent (Prostakath®) also became clearly encrusted during incubation. Clinically the rate of encrustation of Prostakath® has been of about the same magnitude as that of stainless steel stents. It is possible that as long as the gold coating is intact, it will effectively protect the steel substrate from contact with body fluids and thus from encrustation. However, if there is a small scratch or other defect in the gold coating, the situation will change drastically. Reports of the clinical use of Memokath® are rare. Encrustation has usually been reported to be associated with UTI (Low and McRae 1998). The amount of encrustation in both metallic stents increases with time. Similarly, El Faqih and coworkers (1991) showed an increase in encrustation with duration of ureteral stenting: only 6 % of stents were encrusted at six weeks, whereas encrustation rates up to 58-76 % have been reported with ureteric stents indwelling more than 12 weeks.

Bacterial infection is known to be an important factor in the development of encrustation on urinary catheters (Gorman and Tunney 1997). Encrustations harbour a bacterial biofilm, which can cause repeated episodes of bacteriuria (Gorman et al 1995). In sterile urine, formation of encrustation on biomaterials appears to be dependent on both urinary constituents and the surface properties of the synthetic material (Ramsey et al 1987). In the present study we were able to standardize the composition of the artificial urine and prevent infection, which made it possible to concentrate on investigation of the properties of the stent materials.

In urethral *in situ* tests no marked encrustations were seen on the surface of the biodegradable SR-PLGA 80/20 or metallic stainless steel stents. This may be explained by the short follow-up time and/or implantation of the metallic stents into the urethral mucosa, where they were no longer in contact with urine. Another reason for the differences found in the *in vitro* and *in situ* tests might be the flow of urine during voiding in the animal experiments, whereas with artificial urine the rinsing effect was milder. In

the urethral *in situ* tests the amount of encrustation was not analysed by SEM and only the macroscopic amount of encrustations was noted.

Stone formation is a common phenomenon associated with metallic stents, where there is an interface between the metal and urine. Holmes and colleagues (1992) showed four types of metallic stent encrustation composed of magnesium ammonium phosphate (struvite) after a 14-day exposure to urine *in vitro*. The deposition of calcium oxalate monohydrate (COM) crystals formed on the stent partially coated with COM crystals by adhesive forces was found to be most important for the acceleration of the encrustation process in metal stents (Barbalias et al 2000). In urethral *in situ* testing no stone formation was seen macroscopically on the stents, urethra or bladder. Similarly no stone formation was found in any of our patients fitted with an SR-PLGA 80/20 spiral stent, not even in those three cases who had a piece of stent in their bladder at the six-month control cystoscopy. It would thus appear that stone formation is not a problem when SR-PLGA 80/20 spiral stents are used in humans.

3. BIOCOMPATIBILITY

Urological practice involves a number of devices, both temporary and permanent indwelling, which come into contact with blood and urine. Biological incompatibility, susceptibility to infection and encrustation and thrombogenicity are the most common causes of urological stent-associated failures.

The bioabsorbable polymers PLA and PGA have proved their good biocompatibility properties as suture materials during a period of over 30 years. The use of die-drawing in the manufacture of helical spiral prostheses induces an internal orientation of polymer macromolecules. As a result, the inner composition of these devices is structured and the degradation rate is reduced. The degradation rate and the concentration of degradation products in the tissues surrounding the implant should be confined to a tolerable level (Bergsma et al 1995). The residues of short-chain polymers from the primary polymerization process may also reduce biocompatibility. The safety of medical devices

must be confirmed by animal experiments. Self-reinforced, poly-L-lactide (SR-PLLA) spirals have shown good biocompatibility with a minimal tissue reaction around the stent in the anterior urethra, whereas spirals of stainless steel have provoked a marked inflammatory reaction (Kemppainen et al 1993). Previously SR-PLLA material has also been shown in cell culture toxicity tests to be atoxic and the same material proved highly biocompatible in rabbit muscle implantation tests (Isotalo et al 1999).

According to the recommendations of the International Standards for safety testing of new materials or new items of old materials, cell culture tests should be run as the first step in evaluation (ISO/DIS 10993-Part 1:1995) and, after passing these, medical devices should be analysed for long-term safety in specific animal tissue implantation tests. However, on the basis of the results of previous work with biodegradable materials, the cell culture analysis was not done with the new SR-PLGA 80/20 material; testing was moved directly to tissue implantation tests. In the present study the rabbit was selected as test animal because its life expectancy sufficed for the test period and its muscular tissue was suitable for multiple implantations. The *in situ* application of a device at the site of intended use is in fact most fruitful in analysis of the biocompatibility and clinical action of a new device and, urethral implantation was therefore, done in the same animals.

The new biodegradable material in urology, SR-PLGA 80/20, showed good biocompatibility properties similar to those of silicone. The reactions to positive controls, latex and organotin-positive PVC were more pronounced. The observed muscle reactions to SR-PLGA 80/20 are in accord with those reported in earlier studies on pure SR-PLLA or SR-PGA (Petas et al 1997c, Isotalo et al 1999c). SR-PLGA 80/20 can thus be regarded as a safe and highly biocompatible material for urological devices. In the urethral *in situ* analysis the degradation and tissue reactions of SR-PLGA 80/20 stents were comparable to or less marked than the tissue reactions induced by metallic devices. Probably due to the fairly short biodegradation time SR-PLGA 80/20 stents did not encroach into the mucosa, whereas after 3 months two out of six steel stents were very deeply implanted in the urethral mucosa. This can be considered a significant advantage and further reduces the tissue effects.

4. BIODEGRADATION AND COMPRESSION STRENGTH PROPERTIES

Our aim was to develop a biodegradable stent with a degradation time of 6 to 8 weeks as required in most indications where temporary stenting is needed in urology. The degradation time of the SR-PLGA 80/20 spiral stent was estimated after *in vitro* analysis to be 2.5 months (Välilä 1998). We demonstrated in the *in vitro* part of the study that the SR-PLGA 80/20 stent maintains its compression force ratio stable for 6 weeks, which is long enough for recovery from prostatic tissue oedema after thermal therapy of the gland. The total degradation time was even longer previously than estimated. After 6 weeks the compression force decreased slowly, being still 12 % of its original at 12 weeks. Although there are forces in the urethra, which compress and tear the stent, the device was still intact in the urethra in most patients at 2 months. At 4 months the stents had already degraded into small fragments and at 6 months they had been completely eliminated. There were three patients who experienced impaired voiding due to too early degradation. The strength retention of the SR-PLGA spiral stent for two months was thus long enough to meet the needs for temporary urinary drainage after ILCP.

5. CLINICAL APPLICATIONS

Although the ILCP procedure was used in this study as a clinical model for prostatic oedema inducing temporary bladder outlet obstruction, the SR-PLGA 80/20 spiral stent would probably work equally well in other treatment modalities inducing temporary tissue swelling (Issa 1996, Campo 1997, Viridi et al 1997). A deep coagulation of the prostatic adenoma is generated in ILCP and no immediate tissue sloughing occurs. Swelling of necrotic tissue during the first postoperative days causes voiding difficulties and an increased risk of urinary retention. Shrinkage takes place within 6-8 weeks after irradiation (Muschter et al 1993, Mueller-Lisse et al 1996) and thus no significant improvement typically occurs until after this time, maximal results being obtained after 2-3 months.

The biodegradable spiral stents have been used with favourable results after visual laser coagulation (Talja et al 1995, Petas et al 1997a, 1997b), interstitial laser coagulation (Petas et al 2000) and transurethral microwave therapy of the prostate (Dahlstrand et al 1997). The results of the present pilot study, where an SR-PLGA 80/20 spiral stent was used in patients undergoing ILCP, are in accord with these reports in terms of efficacy and adverse events.

Some half of our patients experienced irritative voiding symptoms during the first days or weeks after ILCP and insertion of the SR-PLGA 80/20 stent. However, as both ILCP and stent alone may cause irritative symptoms, it was difficult to distinguish which was the contribution of the stent as we had no control group. We suggest, however, that the symptoms were caused mostly by ILCP itself, although the SR-PLGA 80/20 spiral stent probably aggravated them by increasing the intraprostatic pressure, since the symptom score was already decreased at 1-month follow-up compared with the preoperative score even though the stent was still intact at that time.

The postoperative urinary infection rate of 10 % in the present study can be considered low when compared with similar studies where indwelling catheters have been used to drain the urinary bladder and infection rates of 30 % to 50 % have been reported (Boon et al 1994, leRolland et al 1994, Costa et al 1994, Petas et al 1997). The infection rates in this present study were lower than those in studies utilizing metallic stents. Infections after Fabian coil stent insertion vary from 10 % to 44 % (Karaoglan et al 1992, Thomas et al 1993, Braf et al 1996).

Urethral stricture and bladder neck contracture are fairly common complications after all modes of endoscopic treatment of the urinary tract. Stricture frequencies up to 18 % have been reported after TURP (Mebust et al 1989) and the stricture frequency following metallic spiral stenting has been reported to be 4 % (Braf et al 1996). In this series no strictures or urinary tract stones were seen during the 6-month follow-up.

Although we found the SR-PLGA 80/20 spiral stent to be a safe and highly biocompatible device with a degradation time sufficient to cover the need for postprocedure urinary drainage in cases of prostatic oedema, larger randomized studies are needed to test its true value in combination with different mini-invasive treatment modalities inducing prostatic oedema.

6. FUTURE PROSPECTS

The features of an ideal device should include easy manoeuvrability, radio-opacity, ability to relieve intraluminal and extraluminal obstructions, stability after placement, biological inertia, chemical stability in urine, resistance to encrustation and infection, excellent long-term flow, no inducement of irritative symptoms, and availability at an affordable price. In future, intensive study of the polymers themselves and of the manufacturing process will doubtless introduce new features in urethral stents. New biomaterials and new stent design will be essential in further developing and improving the biomaterials used in urinary tract.

Recently, especially the structure of the urethral stents has been a subject of intensive investigation. The most recent design structure of biodegradable urethral stents is woven mesh and preliminary experimental and clinical experiences will soon be available. Ongoing intensive research into bioabsorbable materials and the development of new manufacturing processes will provide a range of new devices for therapy and reconstruction of urogenital organs, also including the upper urinary tract. Controlled clinical studies will be needed to compare the efficacy of the new stent design with other methods in preventing urinary retention after different types of therapies inducing prostatic oedema, as well as in the temporary treatment of patients with urinary retention awaiting surgery. Similarly, controlled studies will be needed to compare biodegradable stents used in the treatment of urethral strictures to other forms of therapy. A special challenge would be to develop a bioactive stent, which could modulate scar formation after optical urethrotomy or have other long-term therapeutic effects in the urinary tract.

SUMMARY

In the development of bioabsorbable stents, the goal is to find the right material and suitable construction and processing methods to create optimal properties for an implant for a specific application. New therapy modes are continuously being accepted, and the use of biodegradable materials in these methods should be intensively investigated. Also the material development of biodegradable polymers will offer new alternatives and better possibilities to tailor material properties for specific applications.

The aim of the present study was to evaluate the viscoelastic memory and expansion, mechanical and encrustation properties of a new biodegradable polylactic copolymer material (I, II, III, IV) and also the safety, feasibility and efficacy of biodegradable urethral stents *in vivo* (III, IV, V).

In the analysis of viscoelastic memory and self-expansion properties the SR-PLGA 80/20 spiral stent proved to have a 100 % *in vitro* expansion rate capacity during three days. The expansion was faster and greater than that of other self-reinforced polymers. The analysis proved that the new helical spiral stent possesses ideal mechanical properties. The compression strength of SR-PLGA started to decrease after 6 weeks and was 35 % of baseline after 8 weeks. The compression strength is suited to most indications for temporary stenting in urology. The encrustation properties of SR-PLGA 80/20 were superior to nitinol and gold plated stainless steel materials. At 8 weeks' follow-up areas covered by encrustation were respectively 0.12 %, 28.4 % and 4.1 %.

The biocompatibility of the SR-PLGA stent material was evaluated in a muscle implantation test according to the recommendations of ISO. In addition, urethral *in situ* implantation of the stents was used in the analysis of biological safety. The biocompatibility properties of the new SR-PLGA 80/20 material proved to be good in both analyse. In the *in situ* study SR-PLGA 80/20 urethral stents started to disintegrate

macroscopically at 2 months and were almost completely degraded by 3 months. No calcification and bladder stone formation was seen in the PLGA group.

In the clinical studies 50 men evincing lower urinary tract symptoms due to benign prostatic hyperplasia underwent ILCP in a pilot study without a control group. The ILCP thermo therapy was performed under spinal anesthesia and an SR-PLGA urethral spiral stent was inserted into the prostatic urethra after the procedure. Expansion and biodegradation properties, voiding and urinary symptoms were analysed at 1, 2, 4 and 6 months thereafter. The stent expanded rapidly and did not shorten in expansion. Voiding commenced on the first postoperative day in all except three patients and in two cases relocation of the stent had to be done. The mean maximum and average flow rates increased while the DAN-PSS-1 symptom score and post-voiding residual urine decreased statistically significantly. The fragmentation of the spiral stent started after 2 months and at 4 months small fragments in prostatic urethra were seen in transrectal ultrasound. At 6 months cystoscopy detected no stent fragments in the prostatic urethra. Five patients (10 %) had asymptomatic urinary infection postoperatively. No urethral strictures or urinary stones were seen during six months' follow-up.

With material and stent configuration selection and manufacture processing the intended, near ideal properties for urinary tract stents could be achieved in this project. The speed and rate of expansion of the new SR-PLGA 80/20 material were sufficient to lock the stent in place and ensure voiding in the case of oedema induced bladder outlet obstruction after ILCP. The strength retention time of more than 2 months was long enough to avoid later impairment of voiding.

By merit of the ideal degradation time the SR-PLGA prostatic stents might prove eminently most suitable for the prevention of postoperative retention after different types of thermal treatment of prostatic hyperplasia or after brachytherapy of prostatic cancer. This kind of stent is also suitable for the testing of voiding problems before other more radical prostatic operations.

CONCLUSIONS

The most important conclusions to be drawn in respect of this new, biodegradable, self-expandable, self-reinforced copolymer of lactic and glycolic acid (SR-PLGA 80/20) helical spiral prostatic stent to be drawn are:

1. The new helical spiral prostatic stent showed good *in vitro* viscoelastic and expansion properties and was thus suitable for clinical use. Clinically the speed and rate of expansion were sufficient to lock the stent firmly in place.
2. The SR-PLGA 80/20 prostatic stent is markedly more resistant to encrustation than metallic stents and remains its compression strength for 6 weeks, which is suitable for most indications for temporary stenting in urology and is thus well suited for clinical use.
3. The SR-PLGA 80/20 material is safe and highly biocompatible in rabbit muscle and urethra *in situ* and can safely be used clinically.
4. The new biodegradable self-expandable SR-PLGA 80/20 spiral prostatic stent proved to be a safe device for the prevention of postoperative urinary retention after ILCP therapy for prostatic hyperplasia. Complications associated with the use of spiral stents were absent or moderate. The new biodegradable helical spiral stent is a safe and highly biocompatible alternative to metallic stents and suprapubic or indwelling catheters to ensure voiding in the case of temporary obstruction caused by prostatic oedema. The degradation time was long enough in all patients to meet the need for post-procedure urinary drainage.

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REFERENCES

- Ala-Opas M, Talja M, Tiitinen J, Hellström P, Heikkinen A and Nurmi M (1993): Prostatikath in urinary outflow obstruction. *Ann Chir Gynaecol* 82: 14-18
- Andersson TF (1951): Techniques for the preservation of three dimensional structure in preparing specimens for the electron microscopy. *Trans NY Acad Sci* 13: 130-134
- Arai Y, Ishitoya S, Okubo K and Suzuki Y (1996): Transurethral laser coagulation for benign prostatic hyperplasia: treatment outcome and quality of life. *Br J Urol* 78: 93-98
- Ash D, Flynn A, Battermann J, de Reijke T, Lavagnini P and Blank L (2000): ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. *Radiotherapy and Oncology* 57: 315-321
- Baert L, Verhamme L, van Poppel H, Vandeursen H and Baert J (1993): Long-term consequences of urethral stents. *J Urol* 150: 853-855
- Bajoria S, Agarwal S, White R, Zafar F and Williams G (1995): Experience with the second generation Urolume prostatic stent. *Br J Urol* 75: 325-327
- Barbalias GA, Bouropoulos C, Vagenas NV, Bouropoulos N, Siablis D, Liatsikos EN, Karnabatidis D and Koutsoukos PG (2000): Encrustation of a metal alloy urinary stent: a mechanistic investigation. *Eur Urol* 38(2): 144-50
- Barnes DG and Yakubu A (1998): Temporary prostatic stenting using the Barnes stent. In *Stenting the urinary tract*, ed. Yachia D, Isis Medical Media, Oxford: 335-338
- Bergsma E, Rozema F, Bos R and de Bruijn W (1993): Foreign body reactions to resorbable poly-L-lactide bone plates and screws used for the fixation of unstable zygomatic fractures. *J Oral Maxillofac Surg* 51: 666-670
- Bergsma JE, Rozema FR, Bos RRM, van Rozendaal AWM, de Jong WH, Teppema JS and Joziase CAP (1995): Biocompatibility and degradation mechanisms of predegraded and non-degraded poly(lactide) implants; an animal study. *Mater in Med* 6: 715-724
- Berry SJ, Coffy DS, Walsh PD and Ewing LL (1984): The development of human prostatic hyperplasia with age. *J. Urol* 132: 474-479

Biological evaluation of medical devices (1995 Part 6 1994): Tests for local effects after implantation. International standard ISO 10993-62

Biological evaluation of medical devices (1995): Part I: Evaluation and testing. Draft International Standard ISO/DIS 10993-1

Boon TA, de Gier RPE, van Venrooij GEPM, van Swol CFP and Verdaasdonk RM (1994): Clinical and urodynamic results six months after "TULIP" laser-prostatectomy. In: Proceedings of the XIth Congress of the European Association of Urology, July 13-16. Abstract 149

Bos RRM, Rozema FR, Boering G, Nijenhuis AJ, Pennings AJ, Verwey AB, Nieuwenhuis P and Jansen HWB (1991): Degradation of and tissue reaction to biodegradable poly-L-lactide for use as internal fixation of fractures: A study in rats. *Biomaterials* 12: 32-36

Braf Z, Chen J, Sofer M and Matzin H (1996): Intraprostatic metal stents (Prostakath and Urospiral): more than 6 years clinical experience with 110 patients. *J Endourol* 10: 555-558

Brosman SA and Tokota K (1991): Transrectal ultrasound guided interstitial radiation therapy for localised prostate cancer. *Urology* 38: 276-372

Campo B, Bergamaschi F, Corrada P and Ordesi G (1997): Transurethral needle ablation (TUNA) of the prostate: a clinical and urodynamic evaluation *Urology* 46(6): 847-850

Choong S and Whitfield H (1997): The validation of a novel in vitro encrustation model and corroboration with in vivo animal studies (abstract) *J Endourol* 11 (Suppl 1):S50

Choong S, Fry C and Whitfield H (1997): The chemical mechanisms underlying encrustation of urinary catheters (abstract) *J Endourol* 11 (Suppl1)S50

Choong SKS and Whitfield HN (2000): Urinary encrustation of alloplastic materials. *J Endourol* 1: 19-23

Colt H and Dumon J (1995): Airway stents, present and future. *Intervent Pulmonol* 3: 465-478

Cormio L, Talja M, Koivusalo A, Mäkisalo H, Wolff H and Ruutu M (1995): Biocompatibility of various indwelling double –J-stents *J Urol* 153: 494-496

Costa FJ (1994): Lomefloxacin prophylaxis in visual laser ablation of the prostate. *Urology* 44: 933-936

Culkin DJ, Price VH, Zitman R, Leidbetter S, Bundrick W, Mata JA, Goel YA and Venable D (1992): Anatomic, functional and pathologic changes from internal ureteral stent placement. *Urology* 40: 385-390

Cutright DE and Hunsuck EE (1972): The repair of fractures of the orbital floor using biodegradable polylactic acid. *Oral Surg* 33: 28-34

Cutright DE, Perez B, Beasley JD, Larson WJ and Posey WR (1974): Degradation rates of polymers and copolymers of polylactic and polyglycolic acids. *Oral Surg* 37: 142-152

D Ancona FCH, Francisca EAE, Witjes WPJ, Welling L, Debruyne FMJ and de la Rosette JJMCH (1997): High energy thermotherapy versus transurethral resection in the treatment of benign prostatic hyperplasia: Results of a prospective randomized study with 1 year of follow-up. *J Urol* 158: 120-125

Daehlin L, Mohn J, Hoisaeter PA, Hedlund H, Kapstad L, Moen G and Fossberg E (1997): Interstitial laser coagulation in the treatment of benign prostatic hyperplasia: preliminary results. *Tidsskrift for den Norske Laegeforening* 117: 26: 3790-3793

Dahlstrand C, Grundman S and Petterson S (1997): High-energy transurethral microwave therapy for large severely obstructing prostates and the use of biodegradable stents to avoid catheterization after treatment. *Br J Urol* 79: 907-909

Daniels A, Chang M and Andriano K (1990): Mechanical properties of biodegradable polymers and composites proposed for internal fixation of bone. *J Appl Biomater* 1: 57-78

De la Rosette JJ, Muschter R, Lopez MA and Gillat D (1997): Interstitial laser coagulation in the treatment of benign prostatic hyperplasia using diodelaser system with temperature feedback. *Br J Urol* 80: 433-438

Denstedt J, Wollin T and Reid G (1998): Biomaterials used in urology: current issues of biocompatibility, infection and encrustation. *J Endourol* 12: 493-500

Devonec M and Dahlstrand C (1998): Temporary urethral stenting after high-energy transurethral microwave thermotherapy of the prostate. *World J Urol* 16: 120-123

Ditrollo J, Patel P, Watson RA and Irwin JR (2002): Chemo-ablation of the prostate with dehydrated alcohol for the treatment of prostatic obstruction. *J Urol* 167: 2100-2104

Dixon CM (1995): Lasers for the treatment of benign prostatic hyperplasia. *Urol Clin Noth Am* 22: 413-422

Djavan B, Madersbacher S, Klingler C, Ghawidel K, Basharkhah A, Hruby S, Seitz C and Marberger M (1999): Outcome Analysis of Minimally Invasive Treatments for Benign Prostatic Hyperplasia. *Techniques in Urology* 5: 12-20

Doll HA, Black NA, McPherson K, Flood AB, Williams GB and Smith JC (1992): Mortality, morbidity and complications following transurethral resection of the prostate for benign prostatic hypertrophy. *J Urol* 147: 1566-1573

Dominiguez-Gil B, Herrero JC, Carreno , Morales E, Andres A, Aguado JM, Diaz-Conzalez R, Benito A and Morales M (1999): Ureteral stenosis secondary to encrustation by urea-splitting *Corynebacterium urealyticum* in a kidney transplant patient. *Nephrol Dial Transplant* 14: 977-978

Dotter C (1969): Transluminally placed coil springs and arterial tube grafts. Long term patency in the canine popliteal artery. *Invest Radiol* 4: 329-332

Echeverria E and Jimenez J (1970): Evaluation of an absorbable synthetic suture material. *Surg Gyn& Obs* 131: 1-14

El-Faqih S, Shamsuddin A, Chakrabarti A, Atassi R, Kardar A, Osman M and Husain I (1991): Polyurethane internal urethral stents in treatment of stone patients: morbidity related to indwelling times. *J Urol* 146: 1487-1491

Ellis BW and Gidlow AB (1996): Thermoexpandable prostatic stents in frail or elderly men, a risk free and worthwhile technique. *Eur urol* 30 (Suppl2): 110

Entwhistle, KG, Watkinson, AF and Reidy, J (1996): Case Report: migration and shortening of a self-expanding metallic stent complicating the treatment of malignant superior vena cava stenosis. *Clin Radiology* 51: 593-595

Fabian K (1980): Der intraprostatiche Partielle Katheter (Urological Spiral). *Urologe A* 19: 236-238

- Fisher E, Sterzel H and Wegner G (1973): Investigation of the structure of solution grown crystals of lactide copolymers by means of chemical reactions. *Kolloid-Zeitschrift und Zeitschrift für Polymere* 251: 980-990
- Francisca EA, Keijzers GB, d'Ancona FC, Debruyne FM and de la Rosette JJ (1999): Lower-energy thermotherapy in the treatment of benign prostatic hyperplasia: long-term follow-up results of a multicenter international study. *World J Urol* 17: 279-284
- Frazza EJ and Schmitt EE (1971): A new absorbable suture. *J Biomed Mater* 43-58
- Garraway WM, Collins GN and Lee RJ (1991): High prevalence of benign prostatic hypertrophy in the community. *Lancet* 338: 469-471
- Gilding DK (1981): Degradation of polymers: Mechanisms and implications for biomedical applications. In Williams DF ed: *Fundamental Aspects of Biocompatibility* vol 1. Boca Raton, Florida 44-65
- Gilding DK and Reed AM (1979): Biodegradable polymers for use in surgery-poly(glycolic)-poly(lactic acid) homo and copolymers. *Polymer* 20: 1459-1464
- Ginde R and Gupta R (1987): In vitro chemical degradation of poly(glycolic acid) pellets and fibers. *J Appl Polym Sci* 33: 2411-2429
- Glynn RJ, Campion EW, Bouchard GR and Silbert JE (1985): The development of benign prostatic hyperplasia among volunteers in the Normative Aging study. *Am. J. Epidemiol* 121: 78-90
- Gorman S (1995): Addressing clinical needs through biomaterial design. *J Pharmacol* 47: 1060-1061
- Gorman S and Tunney M (1998): Assessment of encrustation behaviour on urinary tract biomaterials. *J Biomat Applic* 12: 136-166
- Goya N, Ishikawa N, Ito F, Ryoji O, Tokumoto T, Toma H and Yamagu Y (1999): Ethanol injection therapy of the prostate for benign prostatic hyperplasia: preliminary report on application of a new technique. *J Urol* 162: 383-386
- Graham DT, Mark GE and Pomeroy A (1983): Cellular toxicity of urinary catheters. *Med J Austral* 55: 456-459
- Graham DT, Mark GE and Pomery AR (1984): In vivo validation of a cell culture test for biocompatibility testing of urinary catheters. *J Biomed Mater Res* 18: 1125-1135

Griffith DP, Musher DM and Itin C (1976): Urease. The primary cause of infection-induced urinary stones. *Invest Urol* 56: 250-254

Guazzoni G, Montorsi F, Coulange C, Milroy E, Pansadoro V, Rubben H, Sarramon JP and Williams G (1994): A modified prostatic Urolume Wallstent for healthy patients with symptomatic benign prostatic hyperplasia: a European multicenter study. *Urology* 44: 364-370

Guess HA (1995): Epidemiology and natural history of benign prostatic hyperplasia. *Urol Clin North Am* 22: 247-261

Hald T, Nordling J, Andersen JT, Bilde T, Meyhoff HH and Walter S (1991): A patient weighted symptom score system in evaluation of uncomplicated benign prostatic hyperplasia. *Scand J Urol Nephrol Suppl* 138: 59-62

Hansen BJ, Flyger H, Mortensen S, Mensink H, Meyhoff HH and the ALFECH study group (1996): I: Symptomatic outcome of transurethral prostatectomy, alpha blockade and placebo in the treatment of benign prostatic hyperplasia. Evaluation of treatment with the Danish Prostatic Symptom score (DAN-PSS-1) system. *The Scand J Urol Nephrol* 30: 103-107

Heino A, Naukkarinen A, Pietilainen T, Merasto ME, Törmälä P, Pohjonen T, Mäkelä EA (1999): Application of a self-reinforced polyglycolic acid (SR-PGA) membrane to the closure of an abdominal fascial defect in rats. *J Biomed Mater Res* 48: 596-601

Herrmann JB, Kelly RJ and Higgins GA (1970): Polyglycolic acid sutures. *Arch. Surg.* 100: 486-490

Hirvensalo E (1990): Absorbable synthetic self-reinforced polymer rods in the fixation of fractures and osteotomies. Academic Thesis, University of Helsinki

Hollinger JO and Battistone GC (1986): Biodegradable bone repair materials. Synthetic polymers and ceramics. *Clin Orthop Rel Res* 207: 290-305

Holmes SAV, Cheng C, Whitfield HN (1992): The development of synthetic polymers that resist encrustation on exposure to urine. *Br J Urol* 69: 651-655

Horninger W, Janetschek G, Watson G, Reissigl A, Strasser H and Bartsch G (1997): Are contact laser, interstitial laser and transurethral ultrasound-guided laser-induced prostatectomy superior to transurethral prostatectomy. *Prostate* 31: 255-263

Hu K and Wallner K (1997): Rectal and urinary morbidity in patients undergoing prostate I-125 implant (abstr). *Int J Radiat Oncol Biol Phys* 39: 292

Isotalo T, Tammela TLJ, Talja M, Välimaa T and Törmälä P (1998): A bioabsorbable self-expandable, self-reinforced poly-L-lactic acid urethral stent for recurrent urethral strictures: A preliminary report. *J Urol* 160: 2033-2036

Isotalo T, Alarakkola E, Talja M, Tammela TLJ, Välimaa T and Törmälä P (1999a): Biocompatibility testing of a new bioabsorbable X-ray positive SR-PLA 96/4 urethral stent. *J Urol* 162: 1764-1767

Isotalo T, Halasz A, Talja M, Tammela TL, Paasimaa S and Törmälä P (1999b): Tissue biocompatibility of a new caprolactone-coated self-reinforced self-expandable poly-L-lactic acid bioabsorbable urethral stent. *J Endourol* 13: 525-530

Isotalo T, Talja M, Tammela TLJ, Törmälä P, Paasimaa S and Andersson L (1999c): Cytotoxicity testing of a new caprolactone-coated self-expanding bioabsorbable self-reinforced poly-L-lactic acid urethral stent. *Urol Res* 27(2): 149-152

Isotalo T, Talja M, Välimaa T, Törmälä P and Tammela TLJ (2000): A pilot study of a bioabsorbable self-reinforced poly L-lactic acid urethral stent combined with finasteride in the treatment of acute urinary retention from benign prostatic enlargement. *BJU Int*, 85: 83-86

Issa MM (1996): Transurethral needle ablation of the prostate: Report of initial United States experience. *J Urol* 156: 413-419

Jacobsen SJ, Jacobson DJ, Girman CJ, Roberts RO, Rhodes T, Guess H and Lieber M (1997): Natural History of prostatism: Risk factors for acute urinary retention. *J Urol* 158: 481-487

Jedwab M and Clerc C (1993): A study of the geometrical and mechanical properties of a self-expanding metallic stent – theory and experiment *J Applied Biomat* 4: 77-85

Kaplan SA and Irving H (1994): Prostatic urethral stents *Semin.Urol.* 12: 193-199

Kaplan SA, Merrill DC, Mosley WG Benson RJ Jr, Chiou RK, Fuselier HA and Parra RO (1993): The titanium intraprostatic stent: the United States experience. *J Urol* 150: 1624-1629

Karaoglan U, Alkibay T, Tokucoglu H , Deniz N and Bozkirli I (1992): Urospiral in benign prostatic hyperplasia. *J Endourol* 6: 455-457

Keane PF, Bonner MC, Johnston SR, Zafar A, Gorman SP (1994): Characterization of biofilm and encrustation on ureteric stents in vivo. *Br J Urol* 73: 687-691

Kemppainen E, Talja M, Riihelä M, Pohjonen T, Törmälä P and Alfthan O (1993): A bioresorbable urethral stent; an experimental study. *Urol Res* 21: 235-238

Kirby RS, Heard SR, Miller, Eardley I, Holmes S, Vale J, Bryan J and Liu S (1992): Use of the ASI titanium stent in the management of bladder outflow obstruction due to benign prostatic hyperplasia. *J Urol* 148: 1195-1197

Kletscher BA and Oesterling JE (1994): Urethral stents: current status for the treatment of recurrent bulbar urethral strictures and benign prostatic hyperplasia. *Current opinion in Urology* 4: 162-167

Kulkarni RK, Pani KC, Neuman C and Leonard F (1966): Polylactic acid for surgical implant. *Arch Surg* 93: 839-843

Kulkarni R, Moore E, Hegyeli A and Leonard F (1971): Biodegradable polylactic acid polymers. *J Biomed Mater Res* 169-181

Lammer J, Hausegger K, Flückiger F, Winkelbauer F, Wildling R, Klein G, Thurnher S and Havelec L (1996): Common bile duct obstruction due to malignancy: treatment with plastic versus metal stents. *Radiology* 201: 167-172

le Rolland B, Barthelemy Y, Colombel M, Chopin D and Abbou CC (1994): TULIP laser in the treatment of benign hypertrophy of the prostate (BPH). In: *Proceedings of the XIth Congress of the European Association of Urology*, July 13-16. Abstract 152

Loshakove A and Azhari H (1997): Mathematical formulation for computing the performance of self expanding helical stent. *Int J Med Inform* 44: 127-133

Losken H, Tschakaloff A, von Oepen, Mooney MP, Moritz O, Michaeli W, Lalikos J and Losken A (1994): Memory of DL-polylactic acid biodegradable plate. *Ann Plastic Surg* 32: 606-611

Low AI, McRae PJ (1998): Use of the Memokath for detrusor-sphincter dyssynergia after spinal cord injury—a cautionary tale. *Spinal Cord* 36(1): 39-44

Löser C and Fölsch U (1996): Self-expanding metallic coil stents for palliation of esophageal carcinoma: two cases of deisive stent dysfunction. *Endoscopy* 28: 514-517

Madersbacher S, Klingler CH, Schatzl G, Schmidbauer CP and Marberger M (1996): The urodynamic impact of transrectal high-intensity focused ultrasound on bladder outflow obstruction. *Eur Urol* 30(4): 437-445

Majola A (1992): Biodegradation, biocompatibility, strength retention and fixation properties of polylactic acid rods and screws in bone tissue. Doctoral Thesis, Helsinki, Finland

Marx M, Bettmann MA, Bridge S, Brodsky G, Boxt LM and Richie JP (1988): The effects of various indwelling ureteral catheter materials on the normal canine ureter. *J Urol* 139: 180-185

McNeill I and Leiper H (1985): Degradation studies of some polyesters and polycarbonates- 2. Polylacide: degradation under isothermal conditions, thermal degradation mechanism and photolysis of polymer. *Polym Degrad Stabil* 11: 309-326

Mebust WK, Holtgrewe HL and Cockett ATK (1989): Transurethral prostatectomy: immediate and postoperative complications. A co-operative study of 13 participating institutions in evaluating 3885 patients. *J Urol* 141: 243-247

Mebust WK, Holtgrewe HL, Cockett AT, Peters PC and writing committee (2002): Transurethral prostatectomy: Immediate and postoperative complications. Cooperative study of 13 participating institutions evaluating 3885 patients. *J Urol* 167: 5-9

Miller RA, Brady JM and Cutright DE (1977): Degradation rates of oral resorbable implants (polylactates and polyglycolates): Rate modification with changes in PLA/PGA copolymer ratios. *Biomed.Mater Res.* 11: 711

Milroy EJ, Chapple CR, Cooper JE, Eldin A, Wallsten H, Seddon AM and Rowles PM (1988): A new treatment for urethral strictures. *Lancet* 1424-1427

Milroy E and Chapple C (1993): The Urolume stent in the management of benign prostatic hyperplasia. *J Urol* 150: 1630-1635

Milroy E and Allen A (1996): Long-term results of UroLume urethral stent for recurrent urethral strictures. *J Urol* 155: 904-908

Montorsi F, Guzzoni G, Bergamaschi F, Consonni P, Galli L and Rigatti P (1994): A comparison of transrectal hyperthermia, transurethral thermotherapy, Urolume Wallstent and prostatic spiral for benign prostatic hyperplasia patients at poor operative risk. *Prostate* 24: 156-161

Mueller-Lisse UG, Heuck AF, Schneede P, Muschter R, Scheidler J, Hofstetter AG and Reiser MF (1996): Postoperative MRI in patients undergoing interstitial laser coagulation thermotherapy of benign prostatic hyperplasia. *J Comp Ass Tom* 20: 2: 273-278

Mulligan ED, Lynch TH, Mulvin D, Greene D, Smith JM and Fitzpatrick JM (1997): High-intensity focused ultrasound in the treatment of benign prostatic hyperplasia. *Br J Urol* 79: 177-180

Multanen M, Välimaa T, Tammela TLJ, Talja M, Seppälä J and Törmälä P (2002): Encrustation of silver nitrate and ofloxacin blended caprolactone-l-lactide coated self-reinforced poly-l-lactic acid urinary tract stents in vitro. *J Endourol* in press

Muschter R, Hofstetter A, Hessel G, Keiditsch E and Schneede P (1992): Interstitial laser prostatectomy – experimental and first clinical results. *J Urol* 147 part II: 346A

Muschter R, Hessel S, Hofstetter A, Keiditsch E, Rothenberger KH, Schneede P and Frank F (1993): Die interstitielle Laserkoagulation in der benignen Prostatahyperplasie. *Urologe* 32: 273-281

Muschter R and Hofstetter A (1995): Technique and results of interstitial laser coagulation. *World J Urol* 14: 109-114

Muschter R and Hofstetter A (1995): Interstitial laser Therapy Outcomes in Benign Prostatic Hyperplasia. *J Endourol* 9: 129-135

Muschter R, de la Rosette JJMCH, Whitfield H, Pellerin JP, Adersbacher S and Gillatt D (1996): Initial human clinical experience with diode laser interstitial treatment of benign prostatic hyperplasia. *Urology* 48: 2: 223-228

Mäkelä EA (1989): Fixation properties and biodegradation of absorbable implants in growing bone. Thesis, University of Helsinki, Finland

Mälkönen P (1989): *Orgaaninen kemia*. Helsinki: Otava 159-162:

Nacey JN, Delahunt B and Tulloch AGS (1985): The assessment of catheter-induced urethritis using an experimental dog model. *J Urol* 134: 623-625

Nakamura T, Hitomi S, Watanabe S, Shimizu Y, Jamshidi K, Hyon SH and Ikada Y (1989): Bioabsorption of polylactides with different molecular properties. *J Biomed Mater Res* 23: 1115-1130

Nakamura K, Baba S, Saito S, Tachibana M and Murai M (1997): Improvement of clinical response by high intensity focused ultrasound for benign prostatic hyperplasia using Sonablate 200. J Urol 157: A433

Nissenkorn I (1995): A simple nonmetal stent for treatment of urethral strictures: a preliminary report. J Urol 154: 1117-1118

Nissenkorn I, Slutzker D and Shalev M (1996): Use of an intraurethral catheter instead of a Foley catheter after laser treatment of benign prostatic hyperplasia. Eur Urol 29: 341-344

Nissenkorn I and Shalev M (1997): Polyurethane stent for treatment of urethral strictures. J Endourol 11: 6: 481-483

Nordling J, Holm HH, Klarskov P, Nielsen KK and Andersen JT (1989): The intraprostatic spiral: a new device for insertion with the patient under local anesthesia and with ultrasonic guidance with 3 months of follow-up. J Urol 142: 756-758

Nordling J, Ovesen H and Poulsen AL (1992): The intraprostatic spiral: clinical results in 150 consecutive patients. J Urol 147(3): 645-647

Oesterling JE (1993): Stenting the male lower urinary tract: a novel idea with much promise. J Urol 150: 1648-1649

Oesterling JE, Kaplan SA, Epstein HB, Defalco AJ, Reddy PK and Chancellor MB (1994): The North American experience with the Urolume endoprosthesis as a treatment for benign prostatic hyperplasia: long-term results . The North American Urolume Study Group. Urology 44: 353-362

Oesterling JE (1995): Benign prostatic hyperplasia. Medical and minimally invasive treatment options. N Engl J Med 33: 99-109

Oosterlinck W and Talja M (2000): Endoscopic urethroplasty with a free graft on a biodegradable polyglycolic acid spiral stent. A new technique. Eur Urol 37: 112-115

Peng T, Gibula P, Yao K, Goosen M (1996): Role of polymers in improving the results of stenting in coronary arteries . Biomaterials 17: 685-694

Pescatore P, Meier-Willerssen H, Manegold B (1997): A severe complication of the new self-expanding spiral nitinol biliary stent. Endoscopy 29: 413-415

Petas A., Talja M., Tammela T, Taari K, Välimäki T, Törmälä P (1995): Bioresorbable PGA-urospiral for preventing urinary retention in VLAP . J Urol 153: 534A

- Petas A , Talja M , Tammela T, Taari K, Välimaa T and Törmälä P (1997a): The biodegradable self-reinforced poly-L-lactic acid spiral stent compared with a suprapubic catheter in the treatment of post-operative urinary retention after visual laser ablation of the prostate. *Br J Urol* 80: 439-443
- Petas A, Talja M, Tammela T, Taari K, Lehtoranta K, Välimaa T and Törmälä P (1997b): A randomized study to compare biodegradable self-reinforced polyglycolic acid spiral stents to suprapubic and indwelling catheters after visual laser ablation of the prostate. *J Urol* 157(1): 173-176
- Petas A, Kärkkäinen P, Talja M, Taari K, Laato M, Välimaa T and Törmälä P (1997c): Effects of biodegradable self-reinforced polyglycolic acid, poly-DL-lactic acid and stainless steel spiral stents on uroepithelium after Nd:YAG laser irradiation of the canine prostate. *Br J Urol* 80(6): 903-907
- Petas A, Vuopio-Varkila J, Siitonen A, Välimaa T, Talja M, Taari K and Törmälä P (1998): Bacterial adherence to self-reinforced polyglycolic acid and self-reinforced polylactic acid 96 stents in vitro. *Biomaterials* 19: 677-681
- Petas A, Isotalo T, Talja M, Tammela TL, Välimaa T and Törmälä P (2000): A randomised study to evaluate the efficacy of a biodegradable stent in the prevention of postoperative urinary retention after interstitial laser coagulation of the prostate. *Scand J Urol Nephrol* 34: 262-266
- Poulsen AL, Schou J, Ovesen H, Nordling J (1993): Memokath: a second generation of intraprostatic spirals. *Br J Urol* 72(3): 331-334
- Prestidge BR, Prete JJ, Buchholz TA, Friedland JL, Stock RG, Grimm PD and Bice WS (1998): A survey of current clinical practice of permanent prostate brachytherapy in the United States. 461-465
- Ramsey JWA, Garnham AJ, Mullhall AB, Crow RA, Bryan JM, Earley I, Vale IA and Whitfield HN (1989): Biofilms, bacteria and bladder catheters: A clinical study. *Br J Urol* 64: 395-398
- Ramsey EW, Miller PD and Parsons K (1997): A novel transurethral microwave thermal ablation system to treat benign prostatic hyperplasia: results of a prospective multicenter clinical trial. *J Urol* 158(1): 112-118

- Reid G, Tieszer C and Lam D (1995): Influence of lactobacilli on the adhesion of *Staphylococcus aureus* and *Candida albicans* to fibers and epithelial cells. *J Ind Microbiol* 15(3): 248-253
- Reid G, Tieszer C, Denstedt JD, Kingston D (1995): Examination of bacterial and encrustation deposition on ureteral stents of differing surface properties, after indwelling in humans. *Coll Surf B: Biointerfaces* 5(abstract) 171-179
- Reid G (1999): Biofilms in infectious disease and on medical devices. *Int J Antimicrob Agents* 11: 223-226
- Ricciotti G, Bozzo W, Perachino M, Pezzica C and Puppo P (1995): Heat expansible permanent intraurethral stents for benign prostatic hyperplasia and urethral strictures. *J Endourol* 9: 417-422
- Rokkanen P, Böstman O, Vainionpää S, Vihtonen K, Törmälä P, Laiho J, Kilpikari J and Tamminmäki M (1985): Biodegradable implants in fracture fixation: early results of treatment of fractures of the ankle. *Lancet* 1: 1422-1424. 1: 1422-1424
- Rokkanen P, Böstman O, Hirvensalo E, Mäkelä EA, Partio E, Pätäälä H, Vihtonen K, Vainionpää S and Törmälä P (1992): Seven-year experience of the use of totally absorbable fracture fixation devices. *Acta Orthop Scand* 63 (Suppl 248) 74
- Rokkanen P, Böstman O, Vainionpää S, Mäkelä EA, Hirvensalo E, Partio EK, Vihtonen K, Pätäälä H and Törmälä P (1996): Absorbable devices in the fixation of fractures. *J Trauma* 40 (Suppl 3) 123-127
- Roos NP, Wennberg JE, Malenka DJ, Fisher ES, McPherson, Andersen TF et al (1989): Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. *N Engl J Med* 320: 1120
- Ruutu M, Alfthan O, Talja M and Andersson L (1985): Cytotoxicity of latex urinary catheters. *B J Urol* 57: 82-87
- Santin M, Motta A, Denyer SP, Cannas M (1999): Effect of the urine conditioning film on ureteral stent encrustation and characterization of its protein composition. *Biomaterials* 20: 1245-1251
- Schatzl G, Madersbacher S, Djavan B, Lang T and Marberger M (2000): Two-year results of transurethral resection of the prostate versus four 'less invasive' treatment options. *Eur Urol* 37: 695-701

- Schatzl G, Temml C, Waldmuller J, Thurridl T, Haidinger G and Madersbacher S (2001): A comparative cross-sectional study of lower urinary tract symptoms in both sexes 40: 213-219
- Schindler A and Harper D (1979): Polylactide II. Viscosity-molecular weight relationships and unperturbed chain dimensions. J Polym Chem Edn 17: 2593-2599
- Schmitt EE and Polistina RA (1967): Surgical sutures. US Pat. 3, 297,033
- Schmitt EE and Polistina RA (1969): Polyglycolic acid prosthetic devices. US Pat. 3, 463, 158
- Schulman CC (2001): Long-term aspects of medical treatment of BPH. Eur Urol 40: 8-12
- Shaw PJ, Milroy EJ, Timoney AG, el Din A and Mitchell N (1990): Permanent external strided sphincter stents in patients with spinal injuries. Br J Urol 66(3): 297-302
- Sinclair R and Preston J (1990): Degradable thermoplastics from lactides. Int. Pat. WO 90/01521.Appl 4
- Slepian M and Yachia D (1998): Urological stents: material, mechanical and functional classification. Edited by D. Yachia. Oxford, UK: Isis Medical Media Ltd 3-10:
- Streitweiser A, Heathcock C and Kosower E (1992): Introduction to organic chemistry, 4 th edn. New York: Macmillan 871-878
- Sullivan LD, McLoughlin MG, Goldenberg LG, Gleave ME and Marich KW (1997): Early experience with high-intensity focused ultrasound for the treatment of benign prostatic hyperplasia Br Urol 79: 172-176
- Talja M, Andersson LC, Ruutu M and Alfthan O (1985): Toxicity testing of urinary catheters. Br J Urol 57: 579
- Talja M, Korpela A and Järvi K (1990): Comparison of urethral reaction to full silicone, hydrogen-coated and siliconised latex catheters. Br J urol 66: 652-657
- Talja M, Tammela T, Petas A, Välimaa T, Taari K, Viherkoski E and Törmälä P (1995): Biodegradable self-reinforced polyglycolic acid spiral stent in prevention of postoperative urinary retention after visual laser ablation of the prostate-laser prostatectomy. J Urol 154: 2089-2092

- Talja M, Välimaa T, Tammela T, Petas A and Törmälä P (1997): Bioabsorbable and biodegradable stents in urology. *J Endourol* 11: 6: 391-397
- Talja M, Multanen M, Välimaa T and Törmälä P (2002): Bioabsorbable SR-PLGA horn stent after antegrade endopyelotomy: a case report. *J Endourol* 16: 299-302 : 299-302
- Taylor G (1987): *Organic chemistry for students of biology and medicine*, 3rd edn. Harlow: Longman Scientific and Technical 211-228
- Terk MD, Stock RG and Stone NN (1998): Identification of patients at increased risk for prolonged urinary retention following radioactive seed implantation of the prostate. *The J Urol* 160: 1379-1382
- Thomas PJ, Britton JP, Harrison NW (1993): The Prostakath stent: four years experience. *Br J Urol* 71: 430-432
- Tunney MM, Jones DS and Gorman SP (1999): Biofilm and biofilm-related encrustation of urinary tract devices. *Methods Enzymol* 310: 558-566
- Törmälä P (1992): Biodegradable self-reinforced composite materials; manufacturing structure and mechanical properties. *Clin Mater* 10: 29-34
- Törmälä P, Pohjonen T and Rokkanen P (1998): Bioabsorbable polymers: materials technology and surgical applications. *Proc Inst Mech Engl* 212: 101
- Wada S, Yoshimura R, Kyo M, Hase T, Masuda C, Watanabe Y, Ikemoto s, Kawashima H and Kishimoto T (2000): Comparative study of transurethral laser prostatectomy versus transurethral electroresection for benign prostatic hyperplasia. *Int J Urol* 7: 373-377
- Vainionpää S, Rokkanen P and Törmälä P (1989): Surgical applications of biodegradable polymers in human tissues. *Progr Polym Sci* 14: 679-716
- Wasson JH, Reda DJ, Bruskewitz RC, Elinson J, Keller AM and Henderson WG (1995): A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. *N Engl J Med* 332: 75
- Vert M, Li S and Garreau H (1992): New insights on the degradation of bioabsorbable polymeric devices based on lactic and glycolic acids. *Clin Mater* 10: 3-8

- Wilksch J, Vernon-Roberts B, Garrett R and Smith K (1983): The role of catheter surface morphology and extractable cytotoxic material in tissue reactions to urethral catheters. *Br J Urol* 55(1): 48-52
- Williams G, Coulange C, Milroy E, Sarramon JP and Rubben H (1993): The Urolume, a permanently implanted prostatic stent for patients at high risk for surgery. *Br J Urol* 72: 335-340
- Williams JC (1996): Interstitial laser coagulation of the prostate. *Tech urol* 2. 3: 130-135
- Wingo PA, Ries LA, Rosenberg HM, Miller DS and Edwards BK (1998): Cancer incidence and mortality 1973-1995: a report card for the US. *Cancer* 82: 1197-1207
- Virdi JS, Pandit A and Sriram R (1997): Transurethral needle ablation of the prostate: A prospective study with a 2-year follow-up. *Br J Urol* 78: A61
- Välimaa T (1995): Bioabsorboituvat materiaalit. Biomateriaalien tutkimuslaitos, Tampereen teknillinen korkeakoulu
- Välimaa T, Talja M, Tammela T, Isotalo T, Petas A, Taari K and Törmälä P (1998): Degradation properties of bioabsorbable self-reinforced self-expanding urological stents. *J Endourology* 12: 148: 6-19
- Välimaa T and Törmälä P (1998): Bioabsorbable materials in urology. In: *Stenting the Urinary System*. Edited by D. Yachia. Oxford, UK: Isis Medical Media Ltd, pp 53-61, Ed D Yachia. Isis Medical Media Ltd, Oxford. ISBN 1899066829
- Välimaa T, Tammela T, Talja M, Isotalo T, Petas A, Taari K ja Törmälä P (1999): Bioabsorboituvien urologisten stenttien laajeneminen. *Urologia Fennica* 13/1/99 ISSN: 1239-1565
- Välimaa T, Talja M, Tammela T, Isotalo T, Petas A, Taari K and Törmälä P (1999): Expansion characteristics of self-reinforced bioabsorbable urethral and prostatic stents. *Eur Urol*, 35 (Suppl 2) 9
- Välimaa T and Törmälä P (2000): Mathematical modelling of expansion characteristics of self-reinforced bio-absorbable stents. *Transactions of Sixth World Biomaterials Congress (May 15-20, Hawaii, USA), vol II* 922
- Yachia D and Beyar M (1991): Temporarily implanted urethral coil stent for the treatment of recurrent urethral strictures: a preliminary report. *J Urol* 146: 1001-100

Yachia D and Aridogan IA (1996): Comparison between first-generation (fixed caliber) and second-generation (self-expanding, large caliber) temporary prostatic stents. *Urol int* 57: 165

Yachia D (1997): Temporary metal stents in bladder outflow obstruction. *J Endourol* 11: 459-465

Zlotta AR, Giannakopoulos X, Maehlum O, Ostrem T and Schulman CC (2003): Long-term Evaluation of Transurethral Needle Ablation of the Prostate (TUNA) for Treatment of Symptomatic Benign Prostatic Hyperplasia: Clinical Outcome up to Five Years from Three Centers. *Eur Urol* 44: 89-93