ANDRES KOTSAR

A Biodegradable Urethral Stent with New Braided Configuration and Drug-eluting Properties

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ACADEMIC DISSERTATION
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University of Tampere, Medical School
Tampere University Hospital, Department of Urology
Finland

Supervised by
Professor Teuvo Tammela
University of Tampere
Finland
Docent, Professor h.c. Martti Talja
University of Kuopio
Finland

Reviewed by
Docent Matti Laato
University of Turku
Finland
Professor Olavi Lukkarinen
University of Oulu
Finland

Distribution
Bookshop TAJU
P.O. Box 617
33014 University of Tampere
Finland

Tel. +358 3 3551 6055
Fax +358 3 3551 7685
taju@uta.fi
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To my son Kristofer

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ABBREVIATIONS

AUR	acute urinary retention
BPH	benign prostatic hyperplasia
BPE	benign prostatic enlargement
BOO	bladder outlet obstruction
DAN-PSS1	Danish Prostate Symptom Score 1
DSD	detrusor-sphincter dyssynergia
HIFU	high intensity focused ultrasound
ELISA	enzyme-linked immunosorbent assay
IL-8	interleukin-8
ILCP	interstitial laser coagulation of prostate
LPS	lipopolysaccharide
LUTS	lower urinary tract symptoms
MCP-1	monocyte chemoattractant protein-1
NSAID	non-steroidal anti-inflammatory drug
PGA	polyglycolic acid
PLA	polylactic acid
PLLA	poly-L-lactic acid
PLGA	copolymer of L-lactide and glycolide acid
RANTES	regulated on activation, normal T-cell expressed and secreted
SEM	standard error of mean
SR	self-reinforced
TGF-β	transforming growth factor-β
TNF-α	tumor necrosis factor-α
THP-1	human acute monocytic leukemia cell line
TRUS	transrectal ultrasound
TUMT	transurethral microwave therapy
TURP	transurethral resection of the prostate
VLAP	visual laser ablation of the prostate

LIST OF ORIGINAL COMMUNICATIONS

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

I Kotsar A., Isotalo T., Mikkonen J. Juuti H., Martikainen P.M., Talja M., Kellomäki M., Törmälä P., Tammela T.L.J.: A New Biodegradable braided self-expandable PLGA prostatic stent: An experimental study in the rabbit. J Endourol 2008 May; 22(5): 1065-9.

II Kotsar A., Isotalo T., Juuti H., Mikkonen J., Leppiniemi J., Hänninen V., Kellomäki M., Talja M., Tammela T.L.J.: Biodegradable braided PLGA urethral stent combined with dutasteride in the treatment of acute urinary retention due to benign prostatic enlargement: a pilot study. BJU Int 2009 Mar; 103(5):626-9.

III Kotsar A., Isotalo T., Uurto I., Mikkonen J., Martikainen P., Talja M., Kellomäki M., Salenius J.-P., Tammela T.: Urethral in situ biocompatibility of new drug-eluting biodegradable stents: an experimental study in the rabbit. BJU Int 2009 Apr; 103(8):1132-5.

IV Kotsar A. Nieminen R., Isotalo T., Mikkonen J., Uurto I., Kellomäki M., Talja M., Moilanen E., Tammela T.L.J.: Biocompatibility of new drug-eluting biodegradable urethral stent materials. Urology, in press.

V Kotsar A. Nieminen R., Isotalo T., Mikkonen J., Uurto I., Kellomäki M., Talja M., Moilanen E., Tammela T.L.J.: Preclinical evaluation of new indomethacin-eluting biodegradable urethral stents. Submitted for publication.

ABSTRACT

The first aim of this study was to evaluate the biocompatibility and degradation as well as potential clinical use of a new biodegradable PLGA (copolymer of L-lactide and glycolide acid) urethral stent with a braided mesh configuration. The second and at the same time, the main objective of this study was to develop a new drug-eluting biodegradable urethral stent. The biocompatibility profile of this new generation stent was tested and analysed in both *in vitro* and *in vivo* experimental studies.

The degradation and biocompatibility profiles of the new braided stent were investigated in an experimental study in 24 male rabbits. Braided PLGA stents were compared with metallic stents *in situ* in the rabbit urethra. PLGA stents of the same configurations were evaluated also in a pilot clinical study in 10 patients combining a urethral stent and dutasteride in the treatment of acute urinary retention due to benign prostatic hyperplasia. The safety, biocompatibility and efficacy of new biodegradable PLGA urethral stent materials with drug-eluting properties were evaluated preclinically using standardized muscle implantation tests in 18 animals and *in situ* urethral biocompatibility testing was conducted in 16 rabbits – with indomethacin, dexamethasone and ciprofloxacine being the primary pharmacological agents examined. Additional studies were carried out with 24 rabbits concentrating on indomethacin-eluting stents. The effect of stent material and the drug-releasing stent material as well as indomethacin itself on cytokine production was studied in THP-1 macrophages. Cytokine production was measured with a protein antibody array. The effect of the stent material was measured on the levels of inflammatory mediators. ELISA was used to confirm the results detected by the protein antibody array and also the effect of indomethacin-releasing stent material and indomethacin itself on the production of cytokines were studied.

In an experimental study in rabbits, the new braided pattern PLGA stents appeared to be more biocompatible than metallic stents and also the degradation process of these stents was well controlled. In the pilot clinical study, the insertion of the stents was successful with a new insertion device and all the patients were able to void after the stent had been implanted. In investigation of the drug-eluting properties of

biodegradable stents, we found biocompatibility profiles similar to pure biodegradable stents and even a decrease in several tissue biological parameters as compared to positive controls. The stent material was found to increase production of IL-8, TNF-α, TGF-β, MCP-1 and RANTES. Interestingly, both indomethacin-releasing stent material as well as indomethacin itself inhibited the production of inflammatory mediators.

The degradation process of the new braided PLGA urethral stents was well controlled and they were more biocompatible than metallic stents. In the clinical study, the new stent overcame the earlier problems of migration and sudden breakage into large particles. However, the mechanical properties still need to be improved. Studies with drug-eluting stents revealed their good biocompatibility properties and that a drug-eluting capacity could be safely incorporated into urethral stents. In this part of the study, the stent material was found to increase the production of inflammatory mediators whereas both indomethacin-releasing stent material and indomethacin decreased the levels of these agents. In conclusion, it is likely that the findings of the present study will be useful in the development of novel drug releasing biomaterials.

1. INTRODUCTION

Since 1980, different types of temporary and permanent stents have been introduced into urological practice to relieve obstruction of the prostatic urethra or the external sphincter and for the treatment of recurrent urethral strictures after internal urethrotomy (Fabian 1980). The devices are divided into permanent and temporary types. The temporary stents are designed primarily for short-term use, usually between four months to three years (Yachia 1997, Shin *et al.* 2006).

There have been rapid developments in manufacturing processes and also the introduction of new biodegradable materials. Biodegradable urethral stents with a spiral configuration have already been tested for the treatment of recurrent urethral strictures (Isotalo *et al.* 1998, Isotalo *et al.* 2002). However these stents did not significantly reduce the epithelial hyperplasia or the recurrence of urethral strictures. The suggestion to start testing drug-eluting stents stemmed from interventional radiology. Drug-eluting stents have been successfully used in endovascular procedures to prevent restenosis due to neointimal hyperplasia (Morice *et al.* 2002, Laroia and Laroia 2004). The drug-eluting stents have revealed significant potential to reduce the development of restenosis after vascular intervention (Vogt *et al.* 2004) and to be able to reduce cardiac events in comparison with the situation with bare metallic stents (Pan *et al.* 2007). This provoked us to start designing a new biodegradable urethral stent with drug-eluting properties to potentially modify the restricturation process in the urethra.

The characteristics of an ideal temporary stent include easy placement under local anaesthesia, minimal local side-effects, such as tissue hyperplasia or encrustation, and a low risk of migration. In addition, endoscopy through the stent should be feasible and the device must be easily removable or, preferably, biodegradable in which case it requires no further surgical intervention. In addition to the material and mechanical properties, urethral stents must also fulfil certain biocompatibility

demands. This present study is one further important step forward in the long process of investigating and developing therapeutically useful biodegradable urological stents.

2. REVIEW OF THE LITERATURE

2.1 Indications for urethral stenting

2.1.1 Bladder outlet obstruction caused by BPH

Benign prostatic hyperplasia is the most common urological condition in men aged ≥ 50 years (Emberton *et al.* 2008) and the main cause of lower urinary tract symptoms (LUTS) in elderly men (Crawford *et al.* 2006). Histologic evidence in the form of both stromal and glandular-epithelial hyperplasia can already be found in approximately 10% of 40-year old men, 60% of men in their 60s and 80% of men in their 80s (Roehrborn *et al.* 1999, Gittelman *et al.* 2006). Although not all these men require treatment, in many it will cause bothersome symptoms that may interfere with activities of daily living, psychological well-being and sexual function and reduce their quality of life (Girman *et al.* 1994). As the disease progresses, the prostate volume tends to increase, maximum urinary flow rate decreases and symptoms worsen. The long-term consequences of the disease may include acute urinary retention and the need for surgery, as well as urinary tract infection, bladder function deterioration, bladder calculi and occasionally renal failure due to obstruction (Barry *et al.* 1997, Jacobsen *et al.* 1997). Among 50-year old men, the lifetime incidence of surgical or medical intervention for BPH is estimated to be 35%. (Oesterling 1996) It has been suggested that acute retention is a relatively common complication of BPH, representing the indication for surgery in 25 to 30% of patients undergoing transurethral resection of the prostate (Holtgrewe *et al.* 1989, Jacobsen *et al.* 1997). Acute urinary retention represents a significant worldwide public health issue, as mortality within the year following an AUR episode appears to be much higher than in the general population, especially in younger patients (Emberton and Fitzpatrick 2008). Recently a tendency has been noticeable favouring less invasive approaches (e.g. pharmacology or catheterization) in treating patients who present with the symptoms, signs or condition of urinary retention

(Kaplan *et al.* 2008). Every urologist who treats elderly men will be faced with patients who ought to undergo surgical treatment but whose comorbidities make surgery an excessively high-risk procedure. Many of the patients will already have reached the stage of acute or chronic retention. In these patients, prostatic stenting offers an alternative to surgery in managing their symptoms.

For diagnostic purposes, stents can be used to predict the outcome of TURP in difficult cases, such as in those with the combination of benign prostatic obstruction and severe detrusor overactivity and urgency urinary incontinence. In patients suffering from Parkinson's disease or multiple sclerosis, there is a substantial risk of de novo or exacerbated postoperative urgency incontinence.

Temporary stents may also be used following acute urinary retention to keep the prostatic urethra open while the size of the prostate is reduced by treatment with 5-alpha-reductase inhibitors such as finasteride or dutasteride (Beisland *et al.* 1992, Gormley *et al.* 1992, Nickel *et al.* 1996). Similarly they can be used while waiting for TURP in case of comorbidity necessiating the postponement of surgery or when there is a long waiting list.

2.1.2 Bladder outlet obstruction caused by prostate cancer

Prostate cancer is a major factor in the health of the aging male population and, in terms of incidence, it is the most common cancer among men in Finland (Finnish Cancer Registry 2007) and also in the United States of America (Merrill and Brawley 1997). Although radical treatment modalities offer the patient with a locally confined disease an excellent opportunity for cure, unfortunately large numbers of newly diagnosed prostate cancer cases are found in the advanced stage of the disease. Prostate cancer was found in 13.3 % of men who presented with acute urinary retention (Moul *et al.* 1989). Hormonal treatment is the treatment of choice in patients who have metastatic or locally advanced disease. After the initiation of hormonal treatment, regression of prostatic mass may take several months. Prostatic stents offer an alternative to the use of an indwelling catheter until the prostatic mass has reduced (Yachia and Aridogan 1996).

2.1.3 Minimally invasive thermal therapies of the prostate

During the last 15 years, a number of mini-invasive treatments for benign prostatic enlargement (BPE) have been introduced, including interstitial laser coagulation of the prostate (ILCP), visual laser ablation of the prostate (VLAP) and high-energy transurethral microwave thermotherapy (TUMT). Most of these techniques induce tissue oedema in the prostate which increases bladder outlet obstruction (BOO) resulting in postoperative urinary retention requiring permanent or intermittent catheterization for up to 6-8 weeks (Madersbacher *et al.* 2004). Similarly, 10-15 % of patients undergoing brachytherapy develop urinary retention either immediately or in the few days following implantation (Terk *et al.* 1998).

Minimally invasive techniques aim to reduce prostate volume by delayed tissue necrosis using relatively low levels of thermal energy and thus reducing the risk of morbidity related to treatment. Unfortunately acute urinary retention is often a temporary consequence of these minimally invasive treatment modalities. Transurethral needle ablation of the prostate (TUNA) uses low-level radiofrequency energy that is delivered by needles into the prostate evoking localized necrotic lesions in the hyperplastic tissue. The most common complication reported is post-treatment urinary retention, occurring at a rate between 13.3% and 41.6%. It can be predicted that within the first 24 hours, about 40% of patients will experience urinary retention (Bruskewitz *et al.* 1998). TUMT devices currently in use elevate the temperatures within the prostate up to 70°C, causing prostate cell death by both necrosis and apoptosis (Barry *et al.* 1997, Brehmer 1997). In the study of Blute et al. (1993), 36% of patients treated with TUMT required catheterization for urinary retention and 63% required catheterization for 1 week or less (Blute *et al.* 1993). Transrectally applied high intensity focused ultrasound (HIFU) is used in the treatment of confined prostate cancer. This technique can elevate the prostate tissue temperature up to 100°C (Madersbacher *et al.* 1995). Mechanisms of action of HIFU involve mechanical interaction of ultrasound waves with tissue, producing coagulating heat, high pressure, cavitation bubbles, and chemically active free radicals that ultimately induce tissue destruction via coagulation necrosis (Chapelon *et al.* 1999). The most common side effect of this procedure is acute urinary retention, occurring in about 20% of patients (Blana *et al.* 2004). In cases of

temporary urinary retention as a consequence of minimally invasive thermal therapy, prostatic stents could again potentially offer an alternative to indwelling catheters.

2.1.4 Neurogenic lower urinary tract disorders

Traumatic, inflammatory, neoplastic, vascular or congenital suprasacral spinal cord lesions are responsible for voiding disorders due to detrusor overactivity and detrusor-sphincter dyssynergia (DSD). The functional obstruction induced by these disorders results in a high-pressure system that can be responsible for genitourinary tract complications. The primary and effective way to treat the condition is drainage with intermittent self-catheterization. Another option, particularly for those patients with poor dexterity, is to reduce the bladder outlet resistance. Transurethral sphincterotomy has been the standard operation to reduce the outflow resistance but it is associated with complications like profuse bleeding and it is not always successful. Stent placement represents a suitable and potentially reversible alternative to the equally effective but irreversible external sphincterotomy (Nambirajan *et al.* 2005, Seoane-Rodriguez *et al.* 2007). Therefore, temporary stents could be used to evaluate whether the patient, will benefit from a reduction in the outlet obstruction. It would also be beneficial in cases when the final outcome of the suprasacral disease causing the lower urinary tract disorder is not clear.

2.1.5 Stenting after urethral stricture surgery

Urethral stricture is one of the oldest known urological diseases and remains a common problem associated with high morbidity (Yelderman and Weaver 1967, Steenkamp *et al.* 1997). The natural history of the condition usually begins with a lesion of the urethral mucosa and infection followed by a scar. The main types of urethral strictures are iatrogenic, inflammatory and traumatic but there are also cases with an unknown aetiology.

Internal urethrotomy is the primary treatment for urethral strictures, but in 40-75% of cases there will be recurrence within 2 years and their treatment involves an even

greater risk of further recurrences (Pitkamäki *et al.* 1992, Isotalo *et al.* 1998). Dilatation and direct-vision internal urethrotomy have been the standard treatments while different kinds of urethroplasty techniques have been used in the most problematic cases. After endoscopic treatment, success rates of 50-60% can be obtained in short strictures without spongiofibrosis but in longer or multiple strictures involving the corpus spongiosum, the recurrence rate is much higher. Higher success rates are also achieved with an iatrogenic stricture than with those of posttraumatic and postinflammatory aetiology (Stone *et al.* 1983). In general, it is advisable to avoid more than two internal urethrotomies in the primary treatment of urethral strictures as the procedure itself induces a local inflammatory reaction which frequently develops a more extensive stricture than the one being treated (Albers *et al.* 1996). Cure rates have not improved by repeat multiple incisions in the circumference of the stricture, glucocorticoid injection into the scar, use of indwelling catheters or postoperative hydraulic self-dilatation. There is a wide range of surgical techniques available for the treatment of urethral strictures including excision of the stricture and replacing or patching the stenosed segment of the urethra with tissue taken from other parts of the body such as skin, bladder and buccal mucosa. Although encouraging results have been reported, these techniques only work in experienced hands.

2.1.5.1 Process of epithelization and urethral wound healing

In general, wound healing is divided into three phases – inflammation, proliferation and maturation (Kirsch and Duckett 2004). The inflammatory phase lasts for up to 7 days, the wound epithelializes and watertightness is achieved. The proliferation phase occurs between 7 and up to 21 days postoperatively with the synthesis and accumulation of collagen by fibroblasts. The final maturation phase lasts about 2 years and is characterized with continued remodeling of collagen. The urethral wall gains 70% tensile strength within 2 weeks (Van Winkle and Hastings 1972). About 7-10 days is necessary for a strong mucosal bridge to form and 3-5 weeks for regeneration of the spongiosum (Wright and Webster 2004). Stricture free healing requires well-approximated, tension-free and water-tight anastomosis. Additional

factors influencing urethral healing are vascularization, the presence of infectious agents and inflammatory compounds.

Urethral stenting can reduce the urine stream on the site. On the other hand it could be argued that the presence of a foreign body can elevate the risk of infections and the stent material itself may act as an inflammatory trigger. Baert et al. (Baert *et al.* 1993) and Verhamme et al. (Verhamme *et al.* 1993) showed fibrotic obliteration of the stent lumen after 22-31 months in a total of four patients with urethral stents. Milroy et al. (Milroy *et al.* 1988) reported hyperplastic urothelial covering of the stent with little underlying inflammation or fibrosis in a study of four dogs implanted with prostatic stents *in situ* for 2-12 months. Bailey et al. (Bailey *et al.* 1998) stated that there was polypoid hyperplasia of the urothelium and underlying connective tissue in 11 of 18 patients with long term urethral stents. In addition, there is always the question of achieving a balance between sufficient urethral luminal diameter for adequate drainage and ischaemic compression of the urethral wall.

2.1.5.2 Effects of inflammatory mediators on epithelial proliferation

There are variety of cytokines and other inflammatory mediators that participate in fibrinogenesis. The blockade of cyclooxygenase (COX) 1 and 2 results in less tissue fibrosis, which is associated with a decrease in the levels of the proinflammatory cytokines and enhancement of the protective cellular processes (Feitoza *et al.* 2008).

TGF-β is an important fibrogenic and immunomodulatory factor that inhibits epithelial cell proliferation (Wahl 1994) and regulates a diverse array of cellular functions including chemotaxis for inflammatory cells (Brandes *et al.* 1991, Reibman *et al.* 1991). TGF-β has also been recently targeted in an attempt to decrease or inhibit the scarring response (Cordeiro *et al.* 1999). Hirschberg et al. reported that loss of local TGF-β was detected in nasal mucosal polyposis compared with healthy nasal mucosa.

Rapala et al. (Rapala *et al.* 1997a) evaluated the effects of interleukin 1 (IL-1) and prostaglandin E2 (PGE2) on experimental granulation tissue in rats by measuring of protein bound 3H-hydroxyproline synthesis. By 7 days postoperatively, IL-1 had decreased the hydroxyproline content of granulation tissue and in this way had decreased the formation of granulation tissue. Rapala and co-workers examined the effects of TNF-α on granulation tissue in rats and showed that after daily applications of TNF-α, the accumulation of collagen hydroxyproline and volume of ingrowth of granulation tissue were significantly lower than in controls (Rapala *et al.* 1997b). An inhibiting effect on the production of collagen was also seen in cultures of human granulation tissue fibroblasts (Rapala *et al.* 1996).

2.1.5.3 Clinical experience in treating stricture recurrence with stents

Stenting or catheterization after urethral stricture surgery is done mainly for two reasons – to support the repair of the urethral wall and to achieve urinary drainage. The mode of action of the urethral stents used so far is based on their mechanical properties. The essential problem is how to prevent the edges of the cut stricture from adhering together and forming a shrinking mass of scar tissue. Many patients are unhappy with the option of repeated self-catheterization to maintain a satisfactory urethral lumen after internal urethrotomy (Niesel *et al.* 1995). In an attempt to solve the problem of recurrence, permanent self-expanding metallic stents, temporarily placed biocompatible metallic stents and polyurethane temporary stents have been introduced into the treatment of urethral strictures. However, at present problems with epithelial hypertrophic proliferation, stent encrustation and difficulties with removal have been associated with both the permanent and temporary endoscopically placed urethral stents (Kletscher and Oesterling 1994). Although preliminary results with biodegradable urethral stents in avoiding urethral stricture recurrence appeared promising (Isotalo *et al.* 1998). When further studies were implemented there was a sense of disappointment (Isotalo *et al.* 2002). Long-term results with more patients did not confirm the initial optimistic outcome. Without a doubt, a significant role was played by the unsatisfactory stent configuration of the helical spiral that caused large fragments to obstruct the urethra

during degradation. However, this was not the only problem, the presence of polyposis was often encountered.

2.2 Urethral stents

2.2.1 Permanent metallic stents

Permanent stents act like a reinforcing cilinder and remain permanently in the wall of the urethra. The era of self-expanding stents in medicine started with the introduction of the braided Wallstent for use in vascular disease, as developed by Hans Wallsten. (Fig.1A)

The concept of using a permanently implanted stent to maintain the patency of a strictured bulbar urethra was first described by Milroy et al. in 1988 (Milroy *et al.* 1988). They were the first to describe the use of the Urolume Wallstent (American Medical Systems, Minnetonka, MN, USA) after dilating the urethra. Soon after the Urolume Wallstent, another mesh stent (knitted) became available: the thermo-expandable Memotherm (C. R. Bard, Murray Hill, NJ, USA). (Fig. 1B) The large caliber and the radical expansion force of these first two stents kept them in place until the stent pushed itself into the urethral wall and epithelialization completely buried it.

The use of Urolume Wallstent or Memotherm was limited to bulbar urethra and they were contraindicated in traumatic strictures. The North American Urolume Trial enrolled 179 patients with recurrent strictures in the bulbar urethra. The initial results were encouraging as insertion of the Urolume stent decreased retreatment rates from 75.3% before insertion to 14.3% after insertion in 105 patients, who were followed for at least 1 year (Badlani *et al.* 1995). Despite the initial optimism, subsequent results were less impressive. Narrowing of the stent lumen was noted in 41.3% of patients. Other long-term complications were painful erection (44%), mucous hyperplasia (44%), recurring stricture (29%), and incontinence (14%). Reports started to appear that the restenosis rates were high in longer-term follow-ups. In addition, these reports also note extreme difficulties in stent removal that

frequently required resection of the entire urethral segment together with the stent and subsequent complex urethroplasty (Wilson *et al.* 2002, De Vocht *et al.* 2003, Shah *et al.* 2003, Gupta and Ansari 2004, Hussain *et al.* 2004). Such difficulties with permanent stents have led to constant increase in interest in retrievable temporary and biodegradable stents.

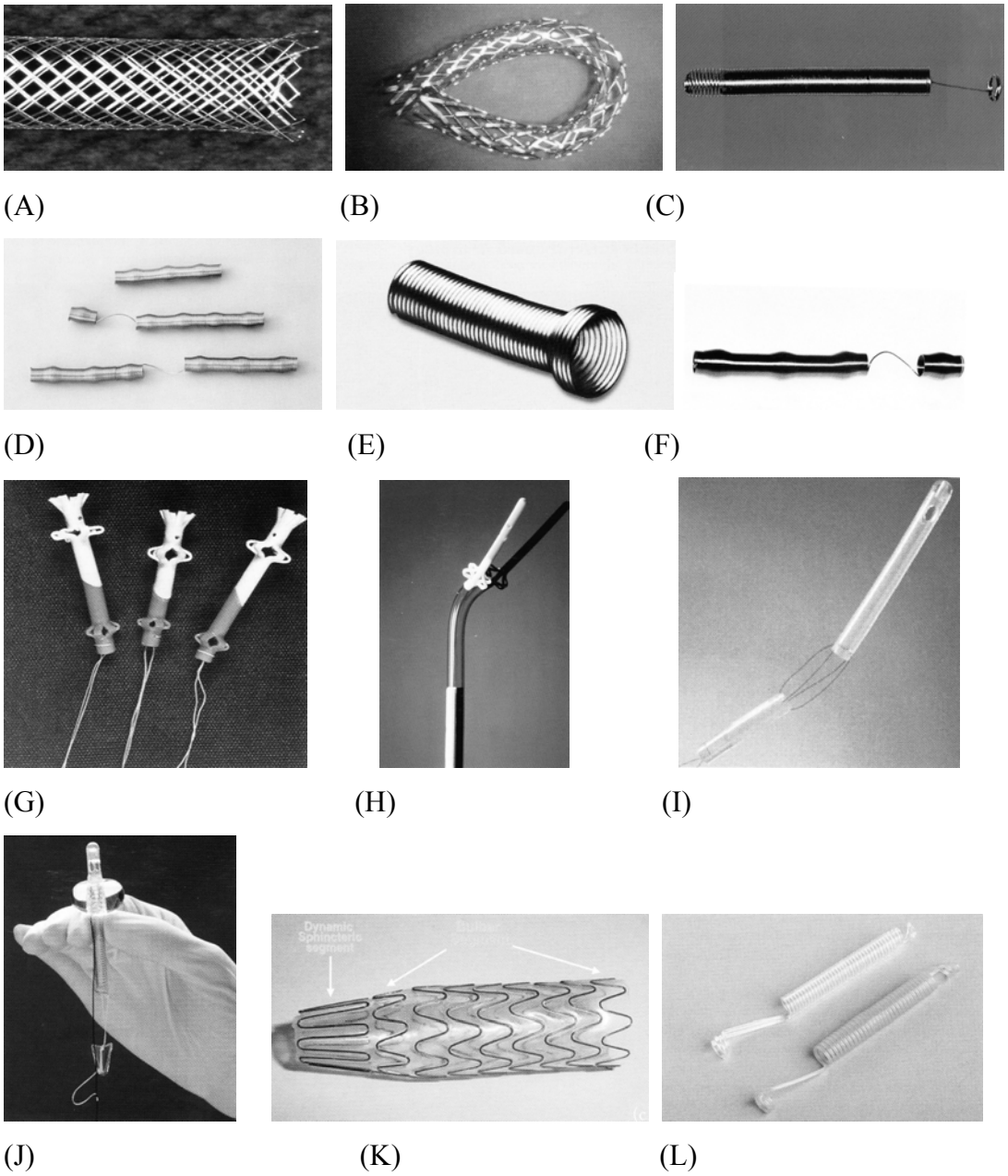

Figure 1. Stents designed for urethral use: (A) Urolume Wallstent. (B) Memotherm. (C) Urospiral. (D) UroCoil System stents. (E) Memokath. (F) ProstaCoil. (G) Nissenkorn intra-urethral catheter. (H) Barnes intra-urethral catheter. (I) Trestle. (J) Spanner. (K) Allium bulbar stent. (L) Biodegradable spiral prostatic stent. (From: Stenting the Urinary System, (2nd ed), Yachia D, Paterson PJ (eds), MD Martin Duniz, London)

2.2.2 Temporary metallic stents

In 1989 the concept of the large-caliber temporary urethral stent was introduced. The new concept was to leave the stent in place only long enough to act as a mold and until there was stabilization of the scarring process. These types of biostable stents are made of various materials including stainless steel, nickel-titanium alloy (nitinol) and polymers. The temporary stents need either to be removed or changed every 4 to 36 months (Yachia 1997, Shin *et al.* 2006). Metallic temporary stents are made of coiled wire. The first generation spiral stents were made of stainless steel and were based on the original Fabian stent (1980). (Fig.1C) They were developed for prostatic obstructions including the stainless steel Urospiral® (1985) and the gold-plated Prostakath® (1985). The second generation spiral stents were made of an alloy of nickel and titanium and were either self- or thermo-expandable.

The initial results with a removable temporary stent UroCoil System® (InStent Inc., Minneapolis, MN, USA) in 18 patients were published in 1991(Yachia and Beyar 1991). (Fig.1D) The temporary UroCoil System® stents were made of a nickel-titanium alloy (Nitinol) and expanded to 24-30 F, with an insertion calibre of 17 F. Urocoils came in three different configurations, allowing their use along the entire urethra, from the bladder neck to the external meatus (Yachia and Beyar 1993, Yachia. 1993). Urocoil stents like Urospiral® and Prostakath® had a long segment to hold the prostatic lumen open, a bulbar segment to anchor the stent in place and a trans-sphincteric spacer connecting the prostatic and bulbar segments (Yachia 1997).

The next urethral stent launched in Europe was Memokath® (Engineers & Doctors, Hornbaek, Denmark) (Soni *et al.* 1994). (Fig.1E) The Memokath® was thermoexpandable and made of nitinol. When the stent was flushed with 50°C water, it expanded at the ends from 24 F to a final diameter of 44 F, anchoring the stent while the main body of the stent remained at 24 F. It was a tightly coiled stent that was designed to prevent urothelial ingrowth. When cooled using water at 10°C, it became soft and pliable, and could be removed with relative ease under local urethral anaesthesia (Perry *et al.* 2002). The alloy was not magnetic and therefore

did not preclude the patient from MRI scanning. It had also excellent biocompatibility properties.

In addition to the use of these stents in urethral strictures, they were also used in the treatment of post-prostate surgery, urethro-vesical anastomotic stenoses (Yachia 2004b). In these cases, a different configuration of the stent ProstaCoil® was inserted into the dilated or incised bladder neck and left indwelling for 1 year before its removal. (Fig. 1F)

The advantage of temporary stents was that they could be used for post-traumatic strictures and in post urethroplasty strictures. The disadvantage of these stents was occlusive hypertrophic scarring that did occur in some UroCoil® and Memokath® stent patients, typically at the ends of the stents.

Yachia et al. have reported the results of 172 patients with recurrent urethral strictures treated with three configurations of UroCoil System® stents (Yachia and Beyar 1991, Yachia 1993, Yachia 2004a). The average indwelling time of the stent was 12 months and average follow-up after stent removal was 36 months. The reported recurrence rates were 17%, 20%, 20% at 2, 3 and 4 years. However, UroCoil System® stents were never approved by the Food and Drug Administration and are no longer commercially available.

2.2.3 Covered metallic stents

Recently, covered retrievable expandable nitinol stents have been introduced for treatment of recurrent urethral strictures (Song *et al.* 2003, Shin *et al.* 2006). The Song urethral stent is woven from a single thread of 0.1 mm-diameter nitinol filament in a tubular configuration and it is covered with polyurethane or polytetrafluoroethylene to prevent tissue hyperplasia ingrowth through the stent wires into the lumen. The removal of the stent, is made possible by presence of 2-mm-diameter nylon loops hooked inside each bend of the distal end of the stent and nylon threads are passed through each of the nylon loops (drawstrings) that fill the inner circumference of the distal stent.

2.2.4 Clinical outcome

Temporary metallic stents are usually inserted under direct cystoscopic visualization using urethral local anaesthesia. The placing of Memokath® stent is not more uncomfortable than cystoscopy until instillation of hot water into the urethra and bladder, which causes discomfort for 4-5 seconds. Most of men inserted the Memokath® stent due to bladder outlet obstruction to the prostatic urethra voided immediately after the procedure so that the outcome of the stent placement was immediately apparent (Perry *et al.* 2002). Although the objective voiding parameters improved immediately after insertion of a nitinol spiral stent, the maximum improvement in quality of the life was not achieved until one month after placement. One explanation for this paradox might be that the stent caused irritation in the trigone (van Dijk *et al.* 2006). When compared to long-term indwelling catheterization, urinary infection was significantly less frequent and less severe in patients with urethral stents (Egilmez *et al.* 2006). The Memokath® intraprostatic stent was concluded to be a valuable addition to the armamentarium of the urologist treating elderly or frail men with advanced BOO and was claimed to complement existing technologies (Perry *et al.* 2002). However, permanent use of stents to relieve benign prostatic obstruction is not indicated in the elective setting (Madersbacher *et al.* 2004).

Placement of a covered retrievable stent for a minimum of four months was effective in inducing long-term resolution of refractory urethral strictures. All patients voided well after stent placement and all reported mild urgency and discomfort at the site of stent placement. These problems resolved spontaneously within one week after stent placement (Choi *et al.* 2007).

In patients suffering from DSD, the implantation of a temporary urethral sphincter stent ensured effective bladder emptying and prevented autonomous and infectious complications (Game *et al.* 2008). After temporary stenting, most patients were subsequently treated with a permanent urethral sphincter stent, while several patients were able to start intermittent self-catheterization later.

2.2.5 Complications associated with temporary metallic stents

One of the problems with temporary self-expanding metallic stents is their shortening by 10-50% depending on the type of stent used. Other common problems are migration of the stent and tissue proliferation into the stent lumen. Migration was a particular problem in the non-expandable first generation spiral stents (10-38%), but there are reports that other temporary stents have exhibited varying high migration rates as well. The thermoexpandable spiral stents have been reported to migrate less often (0-13%) (van Dijk *et al.* 2006). However, even in the newest covered retrievable expandable nitinol stents, the migration remains the largest obstacle to achieving the necessary duration of stent placement critical for achieving long-term resolution (Choi *et al.* 2007).

Haematuria is also a relatively common complication. And this occurs directly after the insertion procedure as a result of small lesions of the urethra caused by delivery manipulation. One explanation for the appearance of later transient haematuria occurring is probably that physical activity causes friction of the stent within the prostatic urethra, leading to damage of the urethral lining. In particular, the stents used for treatment of urethral stricture may develop sphincteric dysfunction when they are deployed in the near vicinity of the external sphincter and they may also induce tissue proliferation at the ends of the stents. When the stent is located in the anterior urethra, it often causes postmicturition dribbling.

The tissue hyperplasia of the urothelium results in luminal narrowing which may cause obstructive symptoms and may necessitate premature removal of the stent. Another relatively common reason for the development of obstruction is also encrustation with calculus formation, which seems to be more of a problem in the spinal cord-injured patient (Perry *et al.* 2002, Mehta and Tophill 2006). Infected urine and high residuals predispose to encrustation and calculus formation. Obviously there are differences between the characteristics of different materials used in the stents. From a clinical point of view, encrustation is a significant problem as it makes removal of the retrievable stents more difficult as well as damaging the urethra.

2.2.6 Polymer stents

As an alternative to metallic stents, several polyurethane stents have been developed. Nissenkorn (1995) 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). (Fig. 1G) Nissenkorn and Shalev treated also urethral stricture patients with a temporary polyurethane stent (Nissenkorn and Shalev 1997). They recommended replacement of the stent once a year in order to prevent encrustations and obstruction.

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 intended to sit at the verumontanum (Barnes and Yakubu 2004). (Fig.1H) The Trestle catheter consists of two silicone tubes with a thread connection. (Fig. 1I) The proximal prostatic part has the Foley catheter design and the distal tube is placed in the bulbous urethra. The Trestle intraurethral catheter has been used in temporary stenting of urethral after high-energy transurethral microwave therapy of the prostate (Devonec and Dahlstrand 1998).

Recently, a novel polyurethane stent (Spanner®) was presented. (Fig. 1J) It is also similar to the proximal 4-6 cm of a Foley catheter, including the proximal balloon to prevent distal placement, a urine port situated cephaled to the balloon, and a reinforced stent of a variable length to span the prostatic urethra (Corica *et al.* 2004). The device is easily inserted and removed, remains anchored in position and significantly improves voiding in patients having obstruction in the prostatic urethra.

Another novel intraurethral catheter is the Surinate Bladder Management System® (Urovalve, Inc, Newark, NJ, USA). The device contains a valve that can be activated by an external magnet for bladder voiding. Preliminary studies showed effective implantation and stability of the device in the urethra but the objectives for use and extraction were not met (Orris *et al.* 2008). CoreFlow® Soft Stent (Prostalund Operations AB, Uppsala, Sweden) is also a recent innovative fusion of a temporary prostatic stent and an indwelling catheter.

2.2.7 Allium urethral stents

The Allium urethral stent was initially designed by Yachia et al. with the Allium corporation in Israel. (Fig. 1K) The prostatic stent has a triangular cross-section as a replica of obstructed prostatic urethral lumen and the bulbar version of the stent has a round cross-section. It consists of a nitinol wire skeleton covered with a biocompatible polymer that is resistant to the urine environment. In the initial study in 24 patients who had recurrent bulbar strictures, the stents were left indwelling for 8 to 14 months and the mean follow-up after stent removal was 20 months (Yachia and Marcovic 2008). Two patients experienced recurrence, one after 12, the other after 18 months.

2.2.8 Biodegradable stents

2.2.8.1 Demands for biodegradable stents

In 1993 the first biodegradable self-reinforced PLLA (poly-L-lactic acid) urethral stent was introduced, and subsequently there has been a rapid development of new materials and configurations of urological stents (Kemppainen *et al.* 1993). An ideal device in the lower urinary tract would provide adequate support to the duct wall, like the urethra, keep the lumen open during and after the healing process, and then biodegrade totally from the body. The material would need to fulfil certain biocompatibility demands according to the guidelines for the tissue biocompatibility analysis and risk assessment of new medical devices. The rigidity of the material would have to be suitable for operating target, the degradation products should be biocompatible metabolic products and the rate of degradation suitable to allow tissue regeneration. The devices also need to have good sterilization properties.

2.2.8.2 Bioabsorption and biodegradation

The term bioabsorbtion means degradation and metabolism of the material *in vivo* into small molecules, like carbon dioxide, water, as well as into energy. The biodegradation means the morphological and chemical degradation of the material

in vivo, and the term degradation represents the general breakdown of the material. The stents used for treatment of urethral strictures in the anterior urethra mostly bioabsorb after being implanted into the tissue, whereas those used in the prostatic urethra biodegrade into small fragments which are then rinsed out with the urine. Degradation of the bioabsorbable polymers is the sum of many factors and is accelerated by the presence of residual monomers and oligomers in the polymer, the alkalinic pH of the surroundings, a reduction in the amount of crystallinity and orientation changes, the presence of certain enzymes e.g. pronase, proteinase-K, and bromeline as well as the sites of implantation where active metabolism, vigourous muscular movements and stresses are loaded on the implant (Talja *et al.* 1997).

2.2.8.3 Biodegradable materials

Polylactide (PLA, polylactic acid) and polyglycolide (PGA, polyglycolic acid) are the most widely used biodegradable materials. They belong to the group of poly-alpha-hydroxy acids which are members of the polyesters.

Lactic acid (2-hydroxypropanoic acid) $CH_3CHOHCOOH$ has two enantiomers, L(+)-lactic acid and D(-)-lactic acid which differ from each other significantly in their rates of biodegradation (Cutright *et al.* 1974). The degradation rate increases when the proportion of D-lactide increases from 0 to 50 mol % (Kulkarni *et al.* 1966). For example, PLA96/4 is a polymer of L-and D- lactide with ratio of 96/4 L- and D-lactic acid, respectively. Also the physical properties of the copolymers depend on the relative amounts of the L and D configurations (Vert *et al.* 1992).

Glycolic acid (2-hydroxyacetic acid) $HOCH_2COOH$ is synthesized by ring opening polymerization from glycolide, resulting in a poly-alpha-hydroxy derivate. Glycolic acid has no chiral centre within the molecule and therefore it does not form enantiomers (Reed *et al.* 1977). Polyglycolide was the first commercially successful synthetic biodegradable polymer to be used as a biomedical material. The great interest of using PGA as device material is due to its good mechanical and absorption properties. The degradation products are normally found in living tissue and are common metabolic products like those of polylactides.

The reaction that produces a polymer from monomers is known as polymerization. A combination of two different monomers can produce a random polymer, a block copolymer, or a graft copolymer. Vicryl® which was discovered in 1975 was the first commercially available copolymer of polylactic acid and polyglycolic acid to be used as a surgical suture. PLGA is a copolymer of lactic and glycolic acid and mostly used with a ratio 80/20 of PLA/PGA. Copolymers are less crystalline than their constituent homopolymers and consequently degrade more rapidly and the increase in the amount of PGA in PLGA accelerates the degradation process.

2.2.8.4 Mechanical properties and degradation of self-reinforced (SR) composite devices

PGA and PLA polymer devices are partially crystalline, linear-chain degradable polymers but they display only modest mechanical strength values. Good mechanical properties can be achieved by using the extrusion and die-drawing techniques (Törmälä 1992). During this self-reinforcing procedure strands from the polymer matrix are formed into aligned molecular chains in the material. These aligned chains form fibrils and filaments, which can carry the forces directed onto the implant. Therefore the fibrous material and matrix material have the same chemical element composition. When the molecular microstructure is oriented, the mechanical strength, modulus, and toughness of the absorbable polymers increase significantly (Törmälä 1992). The mechanical properties are also dependent on the basic molecule and the length of the polymer chains. In addition, the amount of mono- and oligomer residues of polymerisation, the configuration and total mass of the material are important factors in the degradation process (Talja *et al.* 1997).

SR biodegradable stents can be made to be self-expanding at body temperature owing to the viscoelastic memory of the material. The possibility to decide the speed and rate of expansion of stents is of great clinical importance due to the varying requirements for different indications in the use of stents. The level at which the expansion stops as well as the speed of expansion depend on the material, its crystallinity, internal arrangement of molecular chains, initial diameter of the spiral, diameter of the stent wire and annealing temperature (Välimaa *et al.* 2002). The

expansion of the stent to its final diameter may require a time period from 5 minutes to 2 weeks (Talja *et al.* 1997, Välimaa *et al.* 2002). In most urological indications, rapid expansion would be preferable and by using a new tubular mesh configuration the rapid expansion properties can be further improved (Vaajanen *et al.* 2003).

The strength retention time and the functional time of the biodegradable implant vary according to the material selected, the molecular weight, molecular weight distribution and morphology of the polymer and the distribution of repeat units. On the other hand, the process parameters and the sterilization method make their impact on the molecular weight, molecular weight distribution and morphology of the polymer (Törmälä *et al.* 1998). As the degradation rate of the material depends on the moisture content and the temperature, processing, sterilization and storage of these materials should take place in a dry atmosphere and at as low a temperature as possible (Välimaa *et al.* 2002). The biodegradable SR stents have been sterilized either with ethylene oxide or gamma irradiation methods. Since the water solubility of lactide and the glycolide monomer is very high. PLA and PGA degrade by hydrolysis first into short molecular chains (oligomers) and subsequently into basic acids (Nakamura *et al.* 1989). PLLA degrades into L-lactic acid, Poly-D-lactic acid (PDLA) into D-lactic acid, and PGA into glycolic acid.

2.2.8.5 Biocompatibility

Bioabsorbable polymers PLA and PGA have been proven to have good biocompatibility properties as suture materials over a period of 30 years. PGA is well tolerated by the soft tissue, evoking only a minimal inflammatory response (Herrmann *et al.* 1970). The biodegradation of macroscopical SR-PGA implants proceeds by a cellular reaction comparable to the biodegradation reactions seen with polyglycolide sutures (Echeverria and Jimenez 1970). Self-reinforced, poly-L-lactide (SR-PLLA) spirals have shown good biocompatibility evoking only minimal tissue reactions around the stent in the anterior urethra (Kemppainen *et al.* 1993). Biodegradable materials were also found to have similar biocompatibility to that of silicone, and better biocompatibility than latex in an animal toxicity test (Laaksovirta *et al.* 2002b).

2.2.8.6 Encrustation

SR-PLLA stents displayed fewer encrustations than stainless steel stents when implanted in the anterior urethra of the rabbit (Kemppainen *et al.* 1993). Likewise there was some encrustation on gold-plated steel wire (Prostakath®), but none on SR-PGA or SR-PLA 96/4 stents after incubation for two weeks in artificial urine (Cormio *et al.* 1997, Petas *et al.* 1997a). SR-PLGA80/20 stent was also shown to be markedly more resistant to encrustation than metallic urethral stents (Laaksovirta *et al.* 2003). The absence of encrustation in the biodegradable material can be explained by the sloughing off the surface of a biodegradable stent as a consequence of the continuous hydrolysis.

2.2.8.7 Biodegradable prostatic stents

Self-expandable spiral prostatic stents have been developed from different biodegradable materials, including SR-PGA, SR-PLLA, SR-PLA 96/4 with barium and SR-PLGA. (Fig.1L) The configuration of the spiral stent resembles that of the Fabian spiral stent. The outer diameter of the spiral is 7 or 8 mm (Ch 21 or 24), and the prostatic portion 45 to 65 mm long. The neck of the spiral is 20 mm in length.

The biodegradable SR-PGA spiral stents have been used with favourable results after visual laser ablation of the prostate (VLAP) (Petas *et al.* 1997b), interstitial laser coagulation of the prostate (ILCP) (Petas *et al.* 2000) and transurethral microwave therapy of the prostate (TUMT) (Dahlstrand *et al.* 1997). At body temperature, the outer diameter of the spiral stent increases by more than 60% which fixes it in place. The spiral is inserted by pushing it into the prostatic urethra with the tip of the cystoscope immediately after the laser therapy and the patients are then allowed to void immediately. It has been reported that after a SR-PGA stent was inserted, spontaneous voiding occurred in approximately 90% of cases compared with 35% in the group having only a suprapubic catheter after VLAP (Petas *et al.* 1997b, Petas *et al.* 2000). However, the strength retention time of the SR-PGA stents was too short for some patients who reported diminished force of the urinary flow stream at the time of degradation at 3-4 weeks. The total urinary infection rate was lower in the spiral stent group (20%) than in the suprapubic

(35%) or indwelling catheter groups (36%). The DAN-PSS1 weighted symptoms and peak flow rates of the SR-PGA spiral stent groups were comparable to those of the two other groups (Petas *et al.* 1997b, Petas *et al.* 2000). SR-PGA spiral stents have also been used successfully in combination with high energy TUMT therapy to prevent postoperative urinary retention (Dahlstrand *et al.* 1997) as well as a tool to test the risk for post-TURP incontinence in patients with combined benign prostatic obstruction and severe bladder overactivity (Knutson *et al.* 2002).

The *in vitro* degradation of SR-PLA 96/4 spiral stent requires 30 weeks (Välimaa and Törmälä 1996) and it has also been shown to effectively prevent urinary retention in patients undergoing VLAP due to benign prostatic obstruction. The mean degradation time of the SR-PLA 96/4 stent in clinical use was 6 months (Petas *et al.* 1997b).

A SR-PLGA spiral stent was constructed with the aim of developing a biodegradable prostatic stent that would have a degradation time of approximately 2 months. In the *in vitro* experiments, the expansion started rapidly during the first four hours and then continued more slowly during the next three days before it reached 100% (Välimaa *et al.* 2002). In clinical studies where patients underwent ILCP for benign prostate enlargement (BPE) and an SR-PLGA 80/20 spiral stent was inserted upon completion of the operation, more than 90% were able to void on the first postoperative day (Laaksovirta *et al.* 2002a). Only in two cases did the stent have to be moved proximally and relocated, whereafter voiding succeeded. At 2 months, the stent was still present and intact in the urethra in all except 3 patients, but at 4 months it had degraded into small fragments and at 6 months it had completely eliminated. Some half of the patients had irritative symptoms caused at least partly by ILCP itself; 10% had asymptomatic UTI postoperatively. The degradation time was long enough in all patients to meet the need for post-procedure urinary drainage.

Biodegradable stents have also been tested in combination with prostate size decreasing finasteride therapy in patients with acute urinary retention (AUR) due to BPE. SR-PLLA was chosen as stent material because it has an approximately one-year biodegradation time, which leaves sufficient time for finasteride therapy to

achieve its maximum effect. In an open, non-randomised pilot study, the combination treatment in 11 men with AUR due to BPE gave promising results in that all the patients started to void spontaneously within 2 weeks and during the mean follow-up of 24 months only 3 patients required surgical treatment (Isotalo *et al.* 2000). However, in a randomised placebo-controlled study enrolling 55 patients with AUR due to BPE, where the indication for the combination therapy was impaired general condition which would have increased the risk in surgery, only 19 patients completed the study (Isotalo *et al.* 2001). The main reason for discontinuation within the first six months was an insufficient therapeutic response whereas subsequently the rapid uncontrolled breakdown of the configuration of the stent caused obstruction, resulting in impaired voiding and increase of LUTS.

2.2.8.8 Biodegradable urethral stents for urethral strictures

Despite the development of endoscopic and reconstructive urology and the use of different urethral stents the recurrence rate of urethral strictures remains a problem. The essential problem is how to prevent the edges of the cut stricture from adhering together and stopping the scar from shrinking after urethrotomy.

A biodegradable self-reinforced PLLA stent with helical spiral configuration was developed to avoid these problems (Isotalo *et al.* 1998). PLLA was chosen as the device material because of its degradation properties and long, one-year, degradation time. In the early experiments, the spiral stent had no expansion properties and it had to be fixed with suture into the urethral wall which reduced its clinical usefulness. As a result of developments in the manufacturing technology, an expandable spiral stent was introduced. The outer diameter of the stent increases 70% from the initial 8 mm (Ch 24). The expansion is fast and most of it occurs during the first 30 minutes and thus there is no need for external fixation of the stent. Although the SR-PLLA spirals were totally covered by urethral epithelium after six months, in clinical use there seemed to be an elevated risk of sudden breakdown of the helical spiral configuration of the stent, leading to transient obstruction of the lower urinary tract (Isotalo *et al.* 1998, Isotalo *et al.* 2002). A new tubular mesh configuration was developed to overcome these problems. (Fig. 2) It

further improved the expansion and degradation properties of the biodegradable urethral stent (Vaajanen *et al.* 2003, Isotalo *et al.* 2005, Isotalo *et al.* 2006). There is, however, still a need to evaluate the mesh stent both experimentally and clinically.

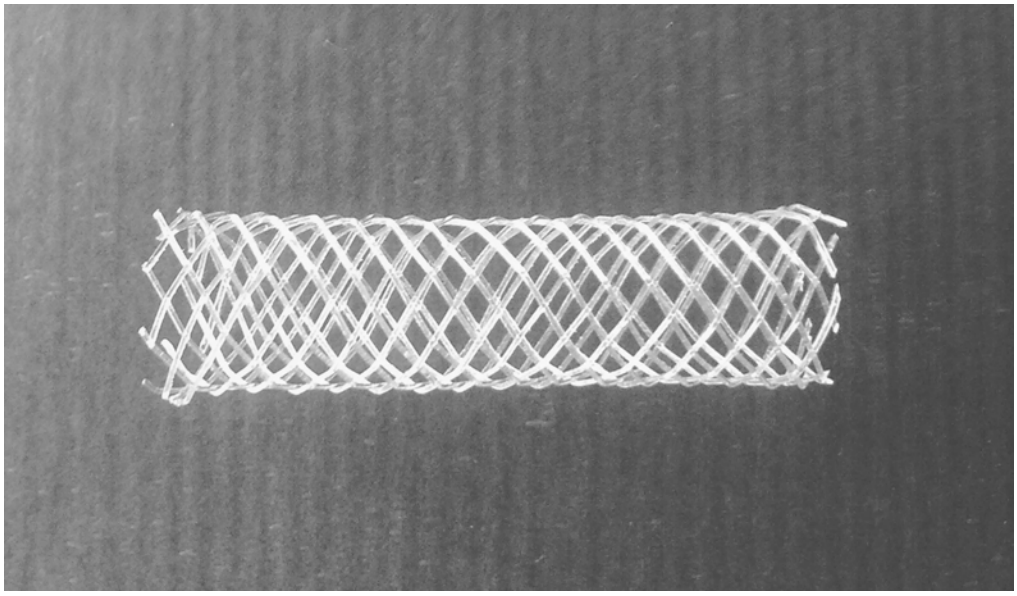

Figure 2. Braided biodegradable urethral stent.

Biodegradable SR-PGA spiral stents have also been used in the free skin urethroplasty for bulbous urethral strictures. The stricture is opened by internal urethrotomy and the preputial free skin graft is mounted over the spiral stent. The graft is located endoscopically and fixed with a percutaneous suture at the site of strictured urethra. Suprapubic urinary diversion is used for ten days. The preliminary results were successful in patients with recurrent bulbous urethral strictures. However, the need for such a long hospitalisation period has, reduced the popularity of the method (Oosterlinck and Talja 2000).

3. AIMS OF THE STUDY

Since the biodegradable stents were first introduced into urological practice, improvements in new materials have been rapid but the ultimate goal of developing the ideal urethral stent still awaits completion.

The general aims of this present study were to evaluate the efficacy of a new braided pattern biodegradable PLGA urethral stent in a clinical setting and to evaluate the degradation and biocompatibility profiles of a new drug-eluting biodegradable PLGA urethral stent *in vitro* and *in vivo*.

The specific aims were

1. To assess the *in situ* degradation and biocompatibility properties of a new braided biodegradable PLGA urethral stent. (I)
2. To evaluate the efficacy and safety of a braided PLGA urethral stent combined with dutasteride in the treatment of acute urinary retention. (II)
3. To define the effect of a biodegradable stent material and a drug-releasing biodegradable stent material on levels of cytokine and other inflammatory mediators. (IV, V)
4. To determine the *in vivo* tissue biocompatibility of a new drug-eluting biodegradable urethral stent materials. (IV)
5. To assess the effect of the drug-eluting properties on the degradation and biocompatibility of braided biodegradable PLGA urethral stents. (III, V)

4. MATERIALS AND METHODS

4.1 Biodegradable materials

The biodegradable stent materials and urethral stents as well as the drug-eluting materials and stents investigated in this study were designed and made at the Institute of Biomedical Engineering, Tampere University of Technology, Finland. The biodegradable material was obtained from Purac Biochem b.v. (Gorinchem, the Netherlands). The biodegradable PLGA stents had an initial monomer ratio of 80:20. The stents were braided using a 1 over 1 pattern. The stents had a final diameter of 6 mm and length of 30 mm (Study I, III, V) or a final diameter of 12 mm and length of 45 mm (Study II). The biodegradable materials and stents were sterilized using γ-irradiation at 25 kGy at 42°C.

In study I, stainless steel fibre manufactured at Erikoisteräs, Ltd., Helsinki, Finland was used for the metallic stents serving as controls. The fibre diameter was 0.2 mm. Metallic stents (Bionx Implants, Ltd., Tampere, Finland) were braided from 16 fibres in a 1 over 1 pattern.

In Study III, the stents were coated by immersion in a solution containing racemic 50L/50D-PLA and one of three drugs, indomethacin, dexamethasone or ciprofloxacin. The mean drug load in the stent was 2.2 mg in indomethacin stents, 2.2 mg in dexamethasone stents and 1.1 mg in ciprofloxacin stents. Stents coated with pure 50L/50D-PLA solution served as controls.

In Study V, the stents were coated with racemic 50L/50D PLA and the coating was blended with two different concentrations of indomethacin. The indomethacin amount in the coating was 699 ± 86 μg (low concentration) and 1943 ± 249 μg (high concentration). Pure 50L/50D PLA coated stents and stents without the coating were used as the control groups.

The material for muscle implantation rods (Study IV) was poly-96L/4D-PLA. The rods were 1.1 mm in diameter and 11 mm in length. The test groups consisted of rods made of 96L/4D-PLA covered with a 50L/50D-PLA coating blended with 2 different concentrations of indomethacin or dexamethasone and rods made of 96L/4D-PLA covered with polycaprolactone blended with simvastatin. The indomethacin amount in the coating was 1.10 ± 0.13 mg (high concentration) and 0.51 ± 0.06 mg (low concentration). The corresponding amounts of dexamethasone were 0.57 ± 0.19 and 0.21 ± 0.04 mg. The drug amount in the simvastatin rods was 0.57 ± 0.13 mg. Rods with pure PCL coating and rods with 50L/50D-PLA coating were used as control groups. Pure silicone rods were used as negative controls and rods made from a brand of latex catheter were used as positive controls.

4.2 Clinical trial

The study included 10 men (mean age 75 years, range 62 - 85) with AUR who were referred to the Department of Urology, Tampere University Hospital for operative treatment. The mean prostatic volume was 59.6 (35.4 - 114) ml. Patients were excluded if they had a small prostate (< 30mL), bladder or prostate cancer, a neurogenic bladder or severe renal insufficiency. The study was performed in an outpatient setting and all the patients were released on the same day.

The stent insertion device consisted of a specially designed delivery tube that was combined with 25° cystoscope optics. Xylocaine 2% Gel® (AstraZeneca, United Kingdom Ltd.) was used to anesthetize the urethra in the same way as done routinely before cystoscopy. The stents were delivered into the prostatic urethra under visual control. The location was always verified also with transrectal ultrasound (TRUS). After the stent insertion procedure, the patients were followed in the outpatient setting until spontaneous voiding was verified. Dutasteride (Avodart®, GlaxoSmithKline, United Kingdom) therapy 0.5 mg daily was started in the same day and was maintained throughout the follow-up. The follow-ups were 1 month and 3 months after the insertion of the stent. The patients underwent measurement of the residual urine, TRUS and cystoscopy, if needed.

4.3 Biocompatibility testing

4.3.1 Animal studies

All animal protocols were reviewed and approved by the Institutional Committee for Animal Research and by the Western-Finland Provincial Government. The investigation conformed to the Guide for Care and Use of Laboratory Animals published by the US National Institute of Health.

Study I was performed in 24 male rabbits half of them received biodegradable braided PLGA stents and the other half metallic stents as controls.

Study III was performed in 16 rabbits divided into groups of four: indomethacin, dexamethasone, ciprofloxacin and pure PLGA stents respectively.

In Study IV, a standardized dorsal muscle implantation test was performed in 18 animals each rabbit receiving 8 implants and as described further 8 samples of each study material was obtained.

In Study V, we used a total of 24 rabbits. The animals were divided into 4 groups. The first two groups were implanted with indomethacin-eluting stents with the drug at two different concentrations. A high dose (indomethacin high) and a low dose (indomethacin low). The other two groups were formed of rabbits receiving control biodegradable stents either with or without the coating.

The rabbits were anesthetized with medetomidine hydrochloride 0.3 ml/kg i.m. (Domitor® 1 mg/ml, Orion Pharma, Finland) and ketamine hydrochloride 0.3 ml/kg i.m. (Ketalar® 50 mg/ml, Pfizer, USA). All animals received pre-operatively a single dose of orofloxacin 5 mg/kg s.c. (Baytril vet.® 100 mg/ml, Bayer, Germany) for antibacterial prophylaxis. After the follow-up the animals were sacrificed using medetomidine hydrochloride 0.3 ml/kg i.m. and ketamine hydrochloride 0.3 ml/kg i.m. as sedation and an overdose of pentobarbital sodium i.v. (Mebunat® 60 mg/ml, Orion Pharma, Finland).

4.3.2 Surgical and endoscopical procedures

Studies I, III, V

The full length of the rabbit urethra was dilated with a Hegar probe to a diameter of 6 mm and the stents were inserted into the prostatic urethra with a specially designed delivery system consisting of a simple metallic tube and piston. The outer diameter of the insertion device was 5 mm. The stent was packed into the tube immediately before insertion and released with the piston into the prostatic urethra immediately proximal to the external sphincter. Localization was then assessed endoscopically using a 13 Fr pediatric cystoscope. After the follow-up period, the urethra surrounding the stent was dissected from the animals en bloc. Representative samples, cross sections and sections taken perpendicular to the wall of the urethra were obtained for histological analysis. The tissue blocks were fixed in 10% formalin and embedded in paraffin, and sections cut and stained with hematoxylin and eosin following routine techniques. In studies I and III, a representative sample was also obtained for the optic microscopy analyses and in study V for scanning electron microscopy analyses. In study I, the follow-up time was at 1 week, 1 month, 2 months or 4 months. In study III it was at 1 month and in study V follow-up occurred at 3 weeks and 3 months.

Study IV

A dorsal midline incision was made and the implants were placed under visual control longitudinally on both sides of the dorsal muscle, using a hollow needle (2.0 mm) and pushing with a trocar. Eight rods were implanted in each animal such that each animal had one positive (organotin polyvinylchloride) and one negative rod (silicone) and six rods produced of study materials these being randomly selected according to the ISO standard. The implantation sites were marked in the fascia with 4-0 nonabsorbable polypropylene sutures.

After the follow up, the test specimens with surrounding muscular tissue were excised. After fixation in 10% phosphate-buffered formalin, the samples were embedded in paraffin, sectioned and stained with hematoxylin and eosin. The follow-up times were 3 weeks or 3 months.

4.3.3 Optical microscopy analyses

In studies I and III, the biodegradation process in the stent and the development of epithelial hyperplasia (polyposis) were evaluated by optic microscopy analyses. The amount of polyposis was evaluated semiquantitatively with a score of 0-3.

4.3.4 Scanning electron microscopy analyses

In study V the degradation process in the stent and the development of epithelial hyperplasia (polyposis) was evaluated by scanning electron microscopy at the Department of Electron Microscopy, University of Kuopio, Finland. The amount of polyposis was assessed semiquantitatively on a scale of 0-3.

4.3.5 Histological analyses

All histologic analyses were performed by an experienced pathologist, who was blinded to the origin of the histological samples. The biological response parameters assessed and recorded included acute inflammatory changes (induction of neutrophils), chronic inflammatory changes (induction of lymphocytes and plasma cells), foreign body reactions, fibrosis, calcification, and eosinophilic reactions. Analyses were made according to ISO standards, which do not include statistical analyses (ISO 10993-6). All tissue reactions were scored semiquantitatively according to the following criteria: 0 = no reaction, 1 = mild reaction, 2 = moderate reaction, 3 = severe reaction.

4.4 Pharmacological evaluation

The reagents used in this study were obtained as follows:

4.4.1 Cell culture

Human THP-1 monocyte-macrophage cell line (American Type Culture Collection, Rockville, MD,USA) was cultured at 37°C in a humidified 5 % carbon dioxide

atmosphere in RPMI 1640 medium with 2 mM L-glutamine (Camprex Bioproducts Europe, Verviers, Belgium) adjusted to contain 1.5 g/l sodium bicarbonate, 4.5 g/l glucose, 10 mM HEPES (4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid) and 1.0 mM sodium pyruvate and supplemented with 0.05 mM 2-mercaptoethanol. The culture media contained 10% heat-inactivated fetal bovine serum, 100 U/ml penicillin, 100 μg/ml streptomycin, and 250 ng/ml amphotericin B (all from Gibco, Paisley, United Kingdom). All other reagents were from Sigma Chemical Co. (St. Louis, MO, USA). Cells were seeded on 24-well plates for protein antibody array and ELISA measurements. Monocytes were differentiated into macrophages by PMA (phorbol myristate acetate) administration (100 nM for 72 hours). Indomethacin-releasing stent material was added to the cells at the time cells were seeded and lipopolysaccharide (LPS) was added after 72 hours incubation. At 24 hours after addition of LPS, the culture medium was collected for measurements. Cells without stent material were incubated 72 hours, subsequently LPS and indomethacin were added. Culture medium was collected for measurements 24 hours after LPS.

4.4.2 Protein antibody array

Cytokine concentrations were determined in cell culture media with Human Cytokine Antibody Array V (RayBiotech, Inc., Norcross, GA, USA), which measures 79 cytokines and other inflammatory mediators (Fig.1). The processing protocol provided by the producer was followed. Array membranes (untreated cells and cells with stent material) were processed simultaneously. The array membranes were blocked for 30 minutes in 2 ml of blocking buffer and then incubated with the sample (1 ml) for 2 hours, and washed. The array membranes were incubated overnight at 4°C with biotin-conjugated secondary antibodies and washed. This was followed by 2 hours incubation with 2 ml of peroxidase-labeled streptavidin solution and 2 minutes' incubation with the detection buffer. Each membrane was then exposed for 1 minute and chemiluminescent signals were measured with FluorChem^{TM} 8800 imaging system (Alpha Innotech, San Leandro, CA, USA). The average chemiluminescence of each mediator and control was calculated for all the

treatments separately. The average of positive controls of each treatment was set to 100 and all mediators of the same treatment were compared to that value.

4.4.3 Enzyme-linked immunosorbent assay (ELISA)

Culture medium samples were kept at -20°C until assayed. The concentrations of tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, monocyte chemoattractant protein (MCP)-1, RANTES (regulated on activation, normal T cells expressed and secreted) (R&D Systems, Inc, Minneapolis, MN, USA), and interleukin (IL)-8 (PeliPair ELISA, Sanquin, Amsterdam, the Netherlands) were determined by ELISA according to the manufacturer's instructions. In ELISAs, LPS (10 ng/ml) (Sigma, St Louis, MO, USA) was used as a positive control for production of inflammatory mediators.

4.5 Statistics

Results are expressed as the mean ± standard error of mean (SEM). When appropriate, statistical significance was calculated by analysis of variance followed by Dunnett multiple comparisons test. Differences were considered significant when $P < 0.05$.

5. RESULTS

5.1 Biodegradation

5.1.1 In rabbits (Study I, III and V)

5.1.1.1 Biodegradable braided urethral stents

In the optic microscope analysis, a gradual and smooth degradation process of the tubular mesh structure of the PLGA stent began at 1 month, with only small pieces of stent material left at 2 months. At 4 months, no signs remained of the stent material. The stent degradation process was smooth and well controlled.

5.1.1.2 Drug-eluting biodegradable braided urethral stents

In the optic microscopy analysis, all 3 control stents had degraded in 1 month, as had 3 out of the 4 dexamethasone-coated stents. In the indomethacin- and ciprofloxacine-coated stent groups, the tubular mesh configuration of the stent was still unbroken in 3 out of 4 animals.

Scanning electron microscopy revealed that coating had no effect on the degradation process of the stents. Coating had started to degrade at 3 weeks in the indomethacin-eluting stent group as well as control group. At 3 months, there was practically no stent material left in either group.

5.1.2 In humans (Study II)

At the follow-up 1 month after the insertion, in TRUS it was found that the stents had not migrated from the prostatic urethra. The stent structure was intact and no

large broken fragments were detected. Cystoscopy was performed in two patients who were experiencing high residual urine but this confirmed that the braided mesh structure of the stents was still unbroken.

At the 3 months' follow up of 5 patients, TRUS revealed that all of the stents had started to degrade smoothly, without any migration of the stent or large particles from the target location.

5.2 Biocompatibility

5.2.1 *In vitro* results (Study IV and V)

To investigate the effect of PLA stent material on the production of cytokines and other inflammatory mediators in THP-1 cells, a cytokine antibody array was used to detect levels of 79 mediators from the cell culture medium. (Fig.3) THP-1 cells expressed ten mediators spontaneously. When stent material was added into the cell culture, the expression of five mediators (IL-8, TNF-α, TGF-β, MCP-1 and RANTES) clearly increased. (Fig.4)

In order to confirm changes in cytokine levels detected by the protein antibody array, the concentrations of these five mediators in culture medium were measured also with ELISA. LPS-treatment was used as a positive control to induce the production of inflammatory cytokines. According to the antibody array results, stent material was found to induce the production of IL-8, TNF-α, TGF-β, MCP-1 and RANTES in THP-1 monocyte-macrophages as compared to the situation in control cells also when measured by ELISA. The effects of LPS on cytokine production were many fold higher as compared to effect of stent material. (Table 1)

Interestingly, indomethacin at the concentration of 10 μM was found to inhibit LPS -induced production of MCP-1 and RANTES significantly whereas it did not influence LPS -induced TGF-β production in human THP-1 cells. The effect of

indomethacin-releasing stent material on LPS-induced MCP-1, RANTES and TGF-β production was similar to that of indomethacin in THP-1 cells. (Fig.5)

	A	B	C	D	E	F	G	H	I	J	K
1	Pos	Pos	Pos	Pos	Neg	Neg	ENA-78	GCSF	GM-CSF	GRO	GRO-α
2	I-309	IL-1α	IL-1β	IL-2	IL-3	IL-4	IL-5	IL-6	IL-7	IL-8	IL-10
3	IL-12p40p70	IL-13	IL-15	IFN-γ	MCP-1	MCP-2	MCP-3	MCSF	MDC	MIG	MIP-1β
4	MIP-1δ	RANTES	SCF	SDF-1	TARC	TGF-β1	TNF-α	TNF-β	EGF	IGF-1	Angiogenin
5	Oncostatin M	Thrombopoietin	VEGF	PDGF-BB	Leptin	BDNF	BLC	Ckβ 8-1	Eotaxin	Eotaxin-2	Eotaxin-3
6	FGF-4	FGF-6	FGF-7	FGF-9	Flt-3 Ligand	Fractalkine	GCP-2	GDNF	HGF	IGFBP-1	IGFBP-2
7	IGFBP-3	IGFBP-4	IL-16	IP-10	LIF	LIGHT	MCP-4	MIF	MIP-3α	NAP-2	NT-3
8	NT-4	Osteoprotegerin	PARC	PIGF	TGF-β2	TGF-β3	TIMP-1	TIMP-2	Neg	Pos	Pos

Figure 3. A schematic diagram of the Human Cytokine Antibody Array shows the locations of the controls and the spots of proteins.
(Pos = positive control, Neg = negative control, ENA = epithelial neutrophil activating peptide, GCSF = granulocyte colony-stimulating factor, GM-CSF = granulocyte-macrophage colony-stimulating factor, GRO = growth-related oncogene, I-309 = glycoprotein secreted by T-lymphocytes, IL = interleukin, IFN = interferon, MCP = monocyte chemoattractant protein, MCSF = macrophage colony-stimulating factor, MDC = macrophage-derived chemokine, MIG = monokine induced by interferon gamma, MIP = macrophage inflammatory protein, RANTES = regulated on activation, normal T cells expressed and secreted, SCF = stem cell factor, SDF = stromal cell-derived factor, TARC = thymus and activation regulated chemokine, TGF = transforming growth factor, TNF = tumor necrosis factor, EGF = epidermal growth factor, IGF = insulin-like growth factor, VEGF = vascular endothelial growth factor, PDGF = platelet-derived growth factor, BDNF = brain-derived neurotrophic factor, BLC = B-lymphocyte chemoattractant, Ck = chemokine, FGF = fibroblast growth factor, Flt = Fms-like tyrosine kinase, GCP = granulocyte chemotactic protein, GDNF = glial cell derived neurotrophic factor, HGF = hepatocyte growth factor, IGFBP = insulin-like growth factor binding protein, IP = interferon-gamma-inducible protein, LIF = leukemia inhibitory factor, LIGHT = lymphotoxins, exhibits inducible expression, and competes with HSV glycoprotein D for HVEM, a receptor expressed by T lymphocytes, MIF = macrophage migration inhibitory factor, MIP = macrophage inflammatory protein, NAP = neutrophil activating protein, NT = neurotrophin, PARC = pulmonary and activation-regulated chemokine, PIGF = placental growth factor, TIMP = tissue inhibitor of metalloproteinase)

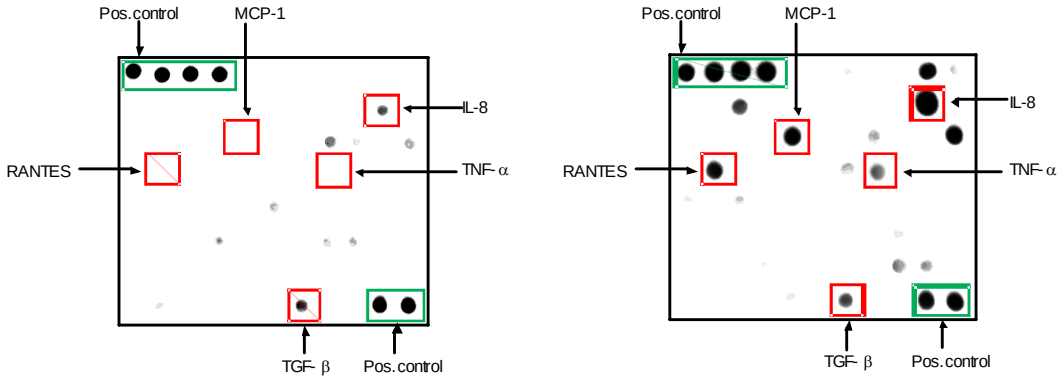

Figure 4. A. Image of the Human Cytokine Antibody Array membrane with culture media from THP-1 cells after 96 hours' incubation. A representative membrane of 4 with similar results.
B. The effect of PLA stent material on inflammatory mediators in THP-1 cells. The protein secretion into the culture medium after 96 hours' incubation was detected by protein antibody array. A representative membrane of 4 with similar results.

Table 1. Effects of stent material and LPS (10 ng/ml) on IL-8, TNF-α, TGF-β, MCP-1 and RANTES production in human THP-1 cells.

Cytokine	Cells	Cells with stent material	LPS-treated cells
IL-8 (ng/ml)	3.7 ± 0.4	21.9 ± 5.2	41.8 ± 5.9
TNF-α (pg/ml)	12.8 ± 0.4	116.7 ± 5.9	298.6 ± 1.1
TGF-β (pg/ml)	61.3 ± 10.0	136.7 ± 12.1	150.9 ± 8.2
MCP-1 (ng/ml)	1.6 ± 0.1	2.3 ± 0.2	3.1 ± 0.2
RANTES (ng/ml)	2.1 ± 0.07	3.7 ± 0.2	5.8 ± 0.6

Mean ± SEM, n=4

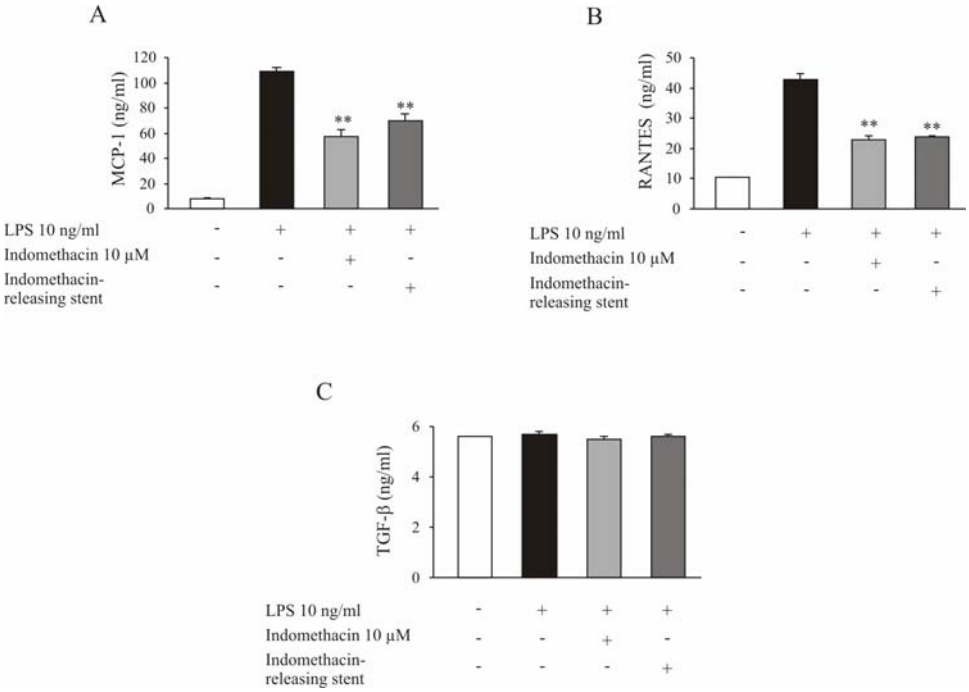

*Figure 5. Effects of indomethacin and indomethacin-releasing stent material on LPS-induced MCP-1 (A), RANTES (B) and TGF-β (C) production in THP-1 cells. Mean ± SEM, n=4. ** indicates P<0.01 as compared with cells treated with LPS alone.*

5.2.2 Biocompatibility in rabbits

5.2.2.1 Braided biodegradable urethral stent (Study I)

The amount of epithelial polyposis evaluated both by optic microscopy and by in the histological analyses increased with time in both stent groups but was clearly greater in the metallic stent group.

The histological analyses revealed evidence of operative trauma, including some epithelial necrosis, in both stent groups at one week. The metallic stents induced more chronic eosinophilic reactions than the biodegradable stents, whereas fibrosis and calcification were slightly more extensive in the biodegradable stent group at 2 months. No calcification was detected in the PLGA group after biodegradation at 4 months. Epithelial oedema was significantly greater in the metallic stent group at all time-points after 1 month.

5.2.2.2 Drug-eluting biodegradable materials and urethral stents (Study III-V)

Polyposis

In Study III, polyposis was equal in the pure PLA-coated and the dexamethasone-coated stents, whereas the indomethacin- and ciprofloxacine-coated stents induced slightly more polyposis.

In study V, we used indomethacin coatings at two different concentrations and at 3 weeks stents containing both the high and the low concentration of indomethacin clearly diminished the amount of epithelial polyposis compared to the pure 50L/50D-PLA coated stent. At 3 months, the amount of polyposis was significantly decreased in all groups and there were no differences between the groups.

Histological tissue reactions

In Study III, all three different drug-releasing stent groups – indomethacin, dexamethasone and ciprofloxacine - induced slightly more eosinophilia than the controls. At the same time, no significant differences in the intensity of acute or chronic inflammatory reactions and fibrosis were noted.

In Study IV at 3 weeks, there was clearly more tissue reactions in all types than at 3 months probably due to the operative trauma. There were no clear differences between the different groups at 3 weeks.

At 3 months, dexamethasone induced more tissue reactions with both drug concentrations than the other materials. At 3 months, fibrosis and chronic inflammatory changes were decreased in the other bioactive groups as well as in the pure biodegradable groups as compared to the positive control group.

In Study V in the histological analyses at 3 weeks, indomethacin-high caused less chronic inflammatory changes than 50L/50D-PLA coated stents whereas indomethacin-low caused slightly more chronic inflammatory changes than 50L/50D-PLA coated stents. Fibrosis could not be seen in indomethacin-low group

whereas indomethacin-high caused slightly more fibrosis than 50L/50D-PLA coated stents. The amount of fibrosis with indomethacin-high was about the same it was with pure PLGA stents. Both concentrations of indomethacin caused clearly more calcification than the control stents. Indomethacin-low had no effect on the amount of eosinophils whereas in the indomethacin-high group, the amount of eosinophils was somewhat higher than in 50L/50D-PLA coated stents group but did not differ from PLGA stent group. There were no acute inflammatory or foreign body reactions found at 3 weeks in any of the groups.

At 3 months, the tissue reactions in all the stent groups were minimal. Both indomethacin stents caused slightly less chronic inflammatory changes and calcification compared to the control 50L/50D-PLA coated stents. Eosinophilia was a little higher in the indomethacin-low stent group but there were no signs of acute inflammatory reactions, fibrosis or foreign body reactions in any of the groups.

5.3 Clinical results (Study II)

The new stent delivery device worked properly and after being released, all the stents stayed firmly in place.

After stent placement, all the patients started to void spontaneously on the same day and their bladders emptied properly. At one month after the placement of the stents, 5 patients were able to void freely with no residual urine or residual urine less than 150 ml. The stent was still found to be located correctly in the prostatic urethra by TRUS. Two patients were voiding spontaneously but still having remarkable residual urine volume. In TRUS, the structure of these stents was seen in place but in cystoscopy the stent lumen was found to be compressed together. These two patients received a suprapubic catheter. Three patients of this pilot study group needed suprapubic or indwelling catheter placement already before one month, one due to a recurrent retention 5 days after stent placement and two due to co-morbidities needing measurement of daily diuresis.

At 3 months, five patients were still voiding without problems, in TRUS the stent was observed to have started to degrade. These patients did not report any local discomfort from the stent during the follow-up. The two patients having high residual urine volume in the first month were still not able to void properly and underwent TURP. None of the patients experienced any migration of the stent or incontinence due to the stent.

6. DISCUSSION

6.1 Braided biodegradable urethral stents

Although the biodegradable stent offers a new and patient convenient option to avoid the use of an indwelling catheter in procedures which cause oedema and postoperative urinary retention, irritative symptoms are common with all stents and they cannot be completely avoided when biodegradable stents are used. In an attempt to minimize the irritating effects of a degradating stent as well as its sudden collapse in the terminal phase of biodegradation, a new configuration of biodegradable urethral stent was developed. The latest design of biodegradable urethral stents is a tubular helical mesh.

It should also be noted that the amount of biodegradable material in braided stents is less than that in the spiral type. The wire diameter is only 0.3 mm compared to 0.8 mm in the helical spiral stents used in similar previous experiments (Laaksovirta *et al.* 2002b). One could predict that with less foreign material in contact with the urethral wall, less tissue irritation and reactions should occur.

In the first studies comparing braided pattern PLGA stents with the metallic ones, we found that although the amount of polyposis increased with time in both stent groups, it was clearly more dominant in the metallic stent group. Initially eosinophilia representing foreign body reactions occurred in both biodegradable and metallic groups but again decreased in the PLGA group towards the end of the degradation time. As the new braided stents showed desirable biocompatibility properties, we decided to perform the first pilot clinical study with the stents designed for human use with the same configuration pattern.

The first serious problem we had to resolve was to develop a suitable instrument for delivering the stent into the desired location in the prostatic urethra. A new

instrument was designed and with its use we succeeded in inserting a biodegradable braided PLGA stent in all the 10 patients in the study group. We were pleased to note that the new stent stayed firmly in place in the location where it was released. More importantly, the stent structure degraded smoothly and no large broken particles were seen to obstruct the urethral lumen. The major setback was the inadequate compression stiffness of these stents that caused the stent to collapse prematurely. One way to avoid this problem in the future is to improve the structure of the stent by adding compression stiffness. Thus further research and developmental work is needed in the field of braided biodegradable urethral stents.

6.2 The concept of developing drug-eluting stents for endourethral use

Since 2002, drug-eluting stents have emerged as the default treatment for many patients with coronary artery disease (Kukreja *et al.* 2008). Drug-eluting stents have truly revolutionized the treatment of coronary artery disease leading to a marked reduction of in-stent restenosis. Due to the excellent clinical results, the first generation drug-eluting stents – the sirolimus-eluting stent and the paclitaxel-eluting stent – are nowadays being selected in preference to bare metal stents for the interventional treatment of symptomatic coronary artery disease (Ako *et al.* 2007). The concept of a drug-eluting stent is fascinating. By controlling the release kinetics of the drug, it can be delivered more to the target location in the organ (Ramcharitar *et al.* 2007). By using biodegradable polymers such as PLA and tyrosine-derived polycarbonates like DTE (desaminotyrosyl-tyrosine-ethyl ester), even more favourable results could be achieved (Tamai *et al.* 2000, Kohn and Zeltinger 2005). The BVS (Bioabsorbable Vascular Solutions, Abbott Vascular Company, Abbott Park, IL, USA) was the first drug-eluting (everolimus) biodegradable stent (Ramcharitar *et al.* 2007, Tanimoto *et al.* 2007).

The success in using drug-eluting stents in interventional radiology and cardiovascular surgery was the inspiration behind the development of this first biodegradable drug-eluting urethral stent. As the biodegradable stent alone was

unable to affect urethral stricture formation, the aim was to design a drug-releasing stent possibly being able to alter the urethral restricturation process.

The development of a new biodegradable drug-eluting stent for endourethral use is a multistep process. Preclinical evaluation of new stent materials and stents is fundamental in demonstrating their safety and equally importantly, their efficacy before any use in human trials could be planned. The use of animal models are necessary when new technologies such as biodegradable drug-eluting urethral stents are to be investigated. For basic biocompatibility testing, the rabbit dorsal muscle implantation test is a standard method (ISO 10993-6). Furthermore, the *in situ* urethral biocompatibility testing provided valuable supplemental information about the stent biocompatibility properties in the target organ. Drugs with anti-inflammatory or antiproliferative activities were chosen as potential bioactive agents suitable for urology. The three drugs chosen were indomethacin, dexamethasone and ciprofloxacin, for incorporation into the stent material to make it drug-eluting.

The drug-eluting properties from biodegradable urethral stent materials were studied by Mikkonen et al (Mikkonen *et al.* 2009). All the studied drugs – dexamethasone, indomethacin and ciprofloxacin - had acceptable release profiles from the biodegradable material so that they potentially could have influenced the processes in the urethral wall. Indomethacin was seen to elute from the stent in two large peaks. The first elution burst was at the beginning and lasted less than 5 days; the second peak was between 30 and 60 days. The study demonstrated that it was possible to achieve sustained elution with indomethacin and the drug elution profile could be fine-tuned.

The first studies we performed with drug-eluting biodegradable materials using dorsal muscle implantation test were encouraging. At the 3 week time point, there was no significant difference in tissue reactions between drug-eluting and pure biodegradable materials. However, at 3 months, there was less fibrosis as well as less extensive chronic inflammatory changes in the drug-eluting stents compared to positive control group. However, we noted an interesting phenomenon in dexamethasone-coated biodegradable materials group - dexamethasone induced more tissue reactions at both tested drug concentrations. A similar finding was also

described by Uurto et al (Uurto *et al.* 2007). Therefore dexamethasone does not appear to represent a promising candidate for incorporation into a drug-eluting biodegradable urethral stent.

We performed two *in situ* urethral biocompatibility studies with drug-eluting stents. In the first study (Study III) at the final follow up point of 1 month, all three drug-eluting stent groups induced slightly more eosinophilia than the controls but there were no significant differences in the other biological reactions assessed. There were equal degrees of polyposis in pure biodegradable and dexamethasone stent groups but slightly more in both indomethacin and ciprofloxacin stents groups. As there are no previously published similar data, we believe that one potential explanation for this phenomenon lies in the drug concentration.

In the next study (Study V) with indomethacin-eluting stents, we used two different drug concentrations in order to define the optimal drug-eluting profiles prior to further studies. When evaluated 3 weeks post-implantation the results were better, i.e. drug-eluting stents containing both high and low concentrations of indomethacin clearly diminished the amount of epithelial hyperplasia as assessed in a scanning electron microscopy study.

In histological analyses at 3 weeks, indomethacin-high caused less chronic inflammatory changes than 50L/50D-PLA coated stents whereas indomethacin-low caused slightly more chronic inflammatory changes than the 50L/50D-PLA coated stents. No fibrosis could be seen in the indomethacin-low group whereas indomethacin-high caused slightly more fibrosis than the 50L/50D-PLA coated stents. The amount of fibrosis with indomethacin-high was about the same as that encountered with pure PLGA stents. At 3 months, the tissue reactions in all stent groups were minimal. Both indomethacin-containing stents caused slightly less chronic inflammatory changes and calcification compared to the control 50L/50D-PLA coated stents. This emphasizes the importance of finding the proper drug-concentration and an optimal drug-release profile is of key importance in the development of a clinically effective biodegradable drug-eluting urethral stent.

One important finding was also that the indomethacin coating had no effect on the degradation process of the stents, which is a benefit when further developing a drug-eluting biodegradable stent.

We demonstrated that the drug-eluting property could be safely incorporated into biodegradable stents and drug-eluting stents. In particular, the indomethacin-eluting stents, proved to be highly biocompatible and certainly worth developing and studying further.

6.3 Pharmacological methodology

Pharmacological methodology was used to investigate the effects of a pure biodegradable material (PLA) and the PLA indomethacin-eluting stent on the production of cytokines and other inflammatory mediators *in vitro*. The goal was to examine the reaction induced by the materials in a more detailed fashion.

Protein antibody array is a modern way to study expression of many mediators simultaneously (Haab 2006). With this method, the results are obtained rapidly and the amount of sample needed is small. The protein antibody array is a useful method in screening tests but the results have to be confirmed by ELISA. Both ELISA and protein arrays are based on antigen-antibody-reaction. Although laboratory techniques for these methods are very well standardized, it should be kept in mind that the reliability of the results depends widely on antibody sensitivities and crossreactivities with other proteins. We confirmed subsequently by ELISA the result that PLA stent material clearly induced the expression of five inflammatory mediators (IL-8, TNF-α, TGF-β, MCP-1 and RANTES) observed in the protein antibody array. Thus, in our hands the results with protein array and ELISA were consistent and confirmed each other.

The effect of indomethacin on inflammatory mediators was tested *in vitro* in THP-1 cells. The indomethacin-releasing stent material and indomethacin had very similar effects on inflammatory mediators, i.e. both inhibited LPS-induced production of two chemotactic factors, MCP-1 and RANTES, that are involved in leukocyte

transmigration. These results led us to conclude that indomethacin had remained active during the stent coating process. The findings are also in accordance with the results from the *in vivo* tests, demonstrating good biocompatibility profile of indomethacin-coated biodegradable stents. The reduced production of the chemotactic factors may explain, at least partly, the decreased development of epithelial polyposis found in the indomethacin-eluting urethral stents.

6.4 A glance into the future clinical aspects

The use of an endoprosthesis to maintain luminal patency is a well-established concept in a variety of surgical specialities, including cardiovascular, gastrointestinal and urological pathologies (Madersbacher 2006). Many issues around urethral stents are still unresolved including the optimal stent design, material and indication. One of the recent large-scale studies of Nitinol prostatic stents by van Dijk and associates proposed that the limitations of prostatic stents make them not suitable for clinical practice (van Dijk *et al.* 2006). However, the diversity of stent designs and indications justifies a more optimistic view (Madersbacher 2006). According to the present BPH guidelines from the European Association of Urology, stents should be only offered as an alternative to permanent or intermittent catheterization in men unfit for invasive treatment (Madersbacher *et al.* 2004). At the moment, prostatic stents have a role in the temporary relief of benign prostatic obstruction (BPO), after minimally invasive therapy not providing immediate relief of obstruction, as a diagnostic tool in some patients with BPO and severe detrusor overactivity with urge incontinence and in frail patients with outflow obstruction due to locally advanced prostate cancer. Although biodegradable prostatic stents offer clear advantages compared with permanent or retrievable stents, the cost of the stent may be a limiting factor for the acceptance of the treatment modality.

Further experimental as well as controlled clinical studies are needed to compare new design biodegradable stents having bioactivity with other methods in the prevention of urinary retention after prostate therapies which induce prostatic oedema as well as in the temporary treatment of patients with urinary retention

awaiting surgery or reduction of prostate volume when started 5α-reductase inhibitor medication.

Although the results with the use of either biostable or biodegradable stents in the treatment of a recurrent stricture especially in the bulbous urethra are in some respects encouraging, there are still a high number of failures. One important reason for this problem is apparently the excessive urethral scarring and periurethral fibrosis in the patients with the most chronic recurrent urethral strictures. Accordingly, it is clear that a biodegradable stent, regardless of its structural configuration, is not capable of preventing urethral stricture recurrence *per se*. The key to solve this dilemma could potentially lie in the development of drug-releasing biodegradable stents which would function like drug-delivery scaffolds to modulate the formation of the scar tissue. Controlled studies are needed to compare these kinds of stents with other forms of therapy in the treatment of urethral strictures.

An intensive effort to discover the best possible stent materials, models, coating materials, and additives of biodegradable stents is continuing. It is anticipated that the findings of the present study will be utilized in the development of novel drug-releasing materials.

7. SUMMARY AND CONCLUSIONS

The first purpose of this study was to evaluate the *in situ* urethral biocompatibility of a new braided pattern biodegradable stent and to assess its efficacy and safety in the pilot clinical study.

In animal studies, the new braided pattern PLGA urethral stent appeared to be safe and showed better biocompatibility properties compared to standard metallic stent.

In the clinical study, the new stent configuration proved to solve the earlier problem of stent migration and sudden breakage into large particles associated with biodegradable spiral stent. However, the mechanical properties still need to be improved to achieve a stent with the desired compression stiffness.

The second part of our study concentrated on the development of a next generation biodegradable urethral stent where a specific drug-releasing property was added to the stent coating.

As in all fields of medical product development, also the new drug-eluting stents have to pass through standardized biocompatibility and safety studies. In the cell culture studies, the stent material was found to increase and both indomethacin-releasing stent material and indomethacin to decrease the production of inflammatory mediators.

Our study demonstrated that drug-eluting biodegradable urethral stents are highly biocompatible and the new drug releasing property does not remarkably affect the degradation time of these stent. Epithelial polyposis and inflammatory changes can be potentially reduced by drug-eluting stents. The indomethacin-eluting stents showed the most promising results and further investigations in urethral stricture

settings are needed to prove or disprove the efficacy of this new indomethacin-eluting biodegradable urethral stent.

The most important conclusions to be drawn from the present findings are:

1. The degradation process of a new braided PLGA urethral stent with tubular mesh configuration was well controlled and took place more smoothly than that seen in stents with a helical configuration.

   The biocompatibility properties of the new braided PLGA urethral stent were excellent.
2. In the clinical study, the fixation of the new braided pattern stents in the prostatic urethra was good, overcoming the earlier problem of stent migration but the mechanical properties were inadequate and need further development.
3. The biodegradable stent material stimulates and indomethacin-releasing stent material inhibits the production of inflammatory mediators.
4. The tissue *in vivo* biocompatibility profile of the new drug-eluting stent materials proved to be good.
5. A drug-eluting capacity can be safely added to biodegradable urethral stents without altering their good biocompatibility profiles and the new drug-releasing property does not remarkably affect the degradation time of the stents.

   Epithelial polyposis and inflammatory changes can be potentially reduced by drug-eluting stents.

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