Review

Biodegradable intestinal stents: A review

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Abstract

Biodegradable stents are an attractive alternative to self-expanding metal stents in the treatment of intestinal strictures. Biodegradable stent can be made of biodegradable polymers and biodegradable metals (magnesium alloys). An overview on current biodegradable intestinal stents is presented. The future trends and perspectives in the development of biodegradable intestinal stents are proposed. For the biodegradable polymer intestinal stents, the clinical trials have shown promising results, although improved design of stents and reduced migration rate are expected. For the biodegradable magnesium intestinal stents, results of preliminary studies indicate magnesium alloys to have good biocompatibility. With many of the key fundamental and practical issues resolved and better methods for adjusting corrosion resistance and progressing biocompatibilities of magnesium alloys, it is possible to use biodegradable intestinal stents made of magnesium alloys in hospital in the not too distant future.
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1. Introduction

Intestinal strictures are a common complication of enteral diseases, including malignant and benign strictures. Malignant strictures include documented malignant obstructions of the duodenum, small bowel, or colorectum. Common malignancies include metastatic disease to the duodenum or proximal jejunum, unresectable cholangiocarcinoma. Benign causes of obstruction include Crohn's disease and anastomotic strictures. Intestinal stents are defined as stents deployed within the small bowel and colon. Metal and plastic stents are useful for treatment of both malignant and benign strictures or fistulas throughout the intestinal tract; however, the use of these stents is associated with several common problems including new stricture formation, perforation, migration, tissue ingrowths and repetitive endoscopic procedures [1]. Uncovered metallic stents induce early mucosal hyperplastic reaction; covered metallic and plastic stents are associated with a higher risk of migration and lower flexibility and shorter/lower radial force [2]. An ideal stent for benign stenoses would be one that has a large diameter, high expansion ratio, axial flexibility, optimal delivery system, withstands ingrowth, maintains luminal integrity, does not cause stent-induced mucosal or parenchymal injury, and does not need a repeat endoscopy for removal [3]. Recently, significant advances have been made in the development of biocompatible and biodegradable materials for medical applications. To overcome the shortcomings of permanent metal and plastic stents, biodegradable stents have been developed. The prolonged dilatory effect before stent absorption and the progressive stent degradation could represent a more favorable solution for patients with benign strictures refractory to standard dilation therapy compared with self-expandable metal and plastic stents, as already shown for esophageal strictures [4,5]. Fig. 1

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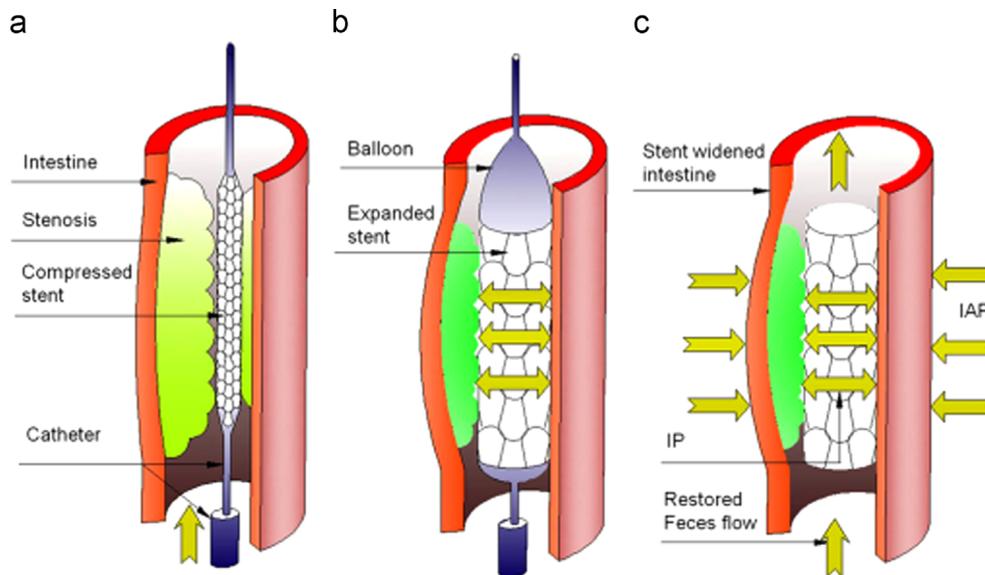
Fig. 1. The diagram of placement process and mechanical function of intestine stent: (a) is the cross-section of the deflated balloon catheter and closed stent inserted into the narrowed intestine; (b) is a balloon inflated, expanding the stent and compressing the tumor to restore the lumen size of the intestine, the stent can be adhesive to the intestinal mucosa; and (c) is the compressed tumor and stent-widened intestine; IP is the intestinal pressure because of the solid feces and movements of intestine, and IAP is the intra-abdominal pressure concealed within the abdominal cavity [32].

shows the process of placement of stent in intestine diagnosed with stenosis.

2. Types of biodegradable materials

2.1. Biodegradable polymers

A biomaterial is defined as any natural or synthetic substance engineered to interact with biological systems in order to direct medical treatment [6]. Biomaterials must be biocompatible meaning which they perform their function with an appropriate host response [7]. Because degradable polymers are able to be broken down and excreted or resorbed without removal or surgical revision, these biomaterials are of utmost interest. Although natural polymers like collagen have been used biomedically for thousands of years, research into biomedical applications of synthetic degradable polymers is relatively new, starting in the 1960s [7]. Biodegradable synthetic polymers offer a number of advantages over other materials for developing scaffolds in tissue engineering. The key advantages include the ability to tailor mechanical properties and degradation kinetics to suit various applications. In addition, the main advantages of synthetic polymers are good biocompatibility, low coefficients of friction, easy processing and workability, ability to change surface chemically and physically, and ability to immobilize cells or biomolecules within them or on the surface [8]. Biodegradable synthetic polymers such as poly(glycolic acid), poly(lactic acid) and their copolymers, poly(p-dioxanone), and copolymers of trimethylene carbonate and glycolide have been used in a number of clinical applications [9]. The major applications include resorbable sutures, stents, drug delivery systems and orthopedic fixation devices such as pins, rods and screws [9].

2.2. Biodegradable magnesium alloys

Traditional metallic materials require minimal corrosion reaction in the body. Over the last decade, a large increase in publications on biodegradable metallic materials has been recorded in both scientific journals and patent databases [10]. Biodegradable metals are defined as metals that are expected to corrode gradually in vivo, with an appropriate host response elicited by released corrosion products, then dissolve completely upon fulfilling the mission to assist with tissue healing with no implant residues [11]. Currently investigated biodegradable metals are mainly magnesium (Mg) and iron (Fe) based alloys, and magnesium alloys are the most intensively studied. Biodegradable magnesium alloys seem to be the suitable biomedical degradable materials. Firstly, magnesium and its alloys are susceptible to dissolution in aqueous solutions, particularly in those containing chloride ion electrolytes because of their very low corrosion potential [12,13]. Secondly, Young's modulus of magnesium alloys is about 45 GPa, which is much closer to that of natural bone (15–20 GPa) [14] than the currently used biomedical metals, such as stainless steel and Nitinol [15]. Therefore the stress shielding effect can be avoided. Thirdly, Mg^{2+} is an essential element and presents in large amount (the fourth most abundant cation) in the human body. The daily intake of Mg for a normal adult is about 300–400 mg and redundant magnesium cations can be harmlessly and efficiently excreted in the urine [16]. Therefore, recently, the study of degradable magnesium alloys has become one of the most revolutionary research topics at the forefront of biomaterials [10,17–20]. Unfortunately, due to this high corrosion rate of magnesium alloys, degradation occurs before the end of healing process. This has become the main limitations of magnesium alloys in

clinical applications [21]. Alloying, novel structure design (ultra-fine grain, bulk metallic glass) and surface modification are effective strategies to improve the corrosion resistance of magnesium alloys [22]. The application of biodegradable magnesium alloy mainly focuses on cardiovascular stents and orthopedic implants. Mg-based absorbable metal stent (AMS, Biotronik, Bülach, Switzerland) are reported to be associated with a high procedural success rate and are well tolerated within different kinds of blood vessels, such as coronary [23,24], pulmonary arteries [25], and lower limb vessels [26,27]. With modifications of chemical composition and strut design to AMS, as well as fast degradable polymer-coating carrier with an anti-proliferative drug, the drug-eluting absorbable metal scaffold (DREAMS, Biotronik, Bülach, Switzerland) showed an increased radial force, a slower degradation rate and promising clinical and angiographic performance in a prospective, multicentre, first-in-man trial (BIOSOLVE-1) [28]. MAGNEZIX® Compression Screw (Syntellix AG Schiffgraben 11, 30159 Hannover, Germany) is a compression screw which can be used for fixing small bones and bone fragments, which is the first magnesium screw product that gets a CE mark. Results of a clinical pilot study revealed that clinically the MAGNEZIX® Compression Screw is equivalent to titanium screw in hallux valgus surgery [29].

3. In vitro and animal test of biodegradable intestinal stents

3.1. Biodegradable polymer intestinal stents

Zilberman et al. [30] investigated the mechanical properties of poly(L-lactide) (PLLA), polydioxanone (PDS), and glycolide-co-ε-caprolactone (PGACL) fibers and stents. Initially, PLLA demonstrated a very high tensile strength (967 MPa) and modulus (5000 MPa) and a moderate ultimate strain (50%), PDS fibers showed moderate tensile strength (583 MPa) and modulus (367 MPa) and high ductility (161%), and PGACL exhibited high tensile strength (721 MPa) and ductility (151%) and moderate modulus (477 MPa). Degradation studies of these fibers indicate that PLLA undergoes slow degradation and can therefore preserve good mechanical properties for 24 weeks. PDS partially preserves its mechanical properties for 6 weeks, whereas the PGACL fiber totally loses its strength after 3 weeks. PDS is a semicrystalline, biodegradable polymer that belongs to the polyester family. PDS monofilament is commercially absorbable surgical suture. It degrades by random hydrolysis of its molecule ester bonds. The degradation accelerates by low pH. The degradation product—glyoxylic acid—is the primary precursor of oxalic acid and is an intermediate in the conversion of glycolic acid to glycine. None of degradation products or intermediates is harmful [31]. The degradation process occurs in two stages. The first involves amorphous regions of the matrix, the second the crystalline areas of the polymer [31,32]. Due to the fact that mechanical and physical properties largely depend on the presence of the crystalline areas, the effect of the degradation is not linear. The stent material is partly absorbed and partly travels through the gastrointestinal system. Li et al. [32] found the weft-knitted PDS stent maintained more than 60% of its original radial force above 12 weeks in PBS. No apparent changes of the stent were found within 8 weeks, while small cracks were observed after 12 weeks, as shown in Fig. 2.

3.2. Biodegradable magnesium intestinal stents

To date, there is no report about prototype of biodegradable magnesium intestinal stents. This is probably due to the limited ductility and poor workability at room temperature resulting from its hexagonal crystal lattice, which leads to the great challenge of processing magnesium wires with small diameter for knitting of stent. However, attempts were carried out and
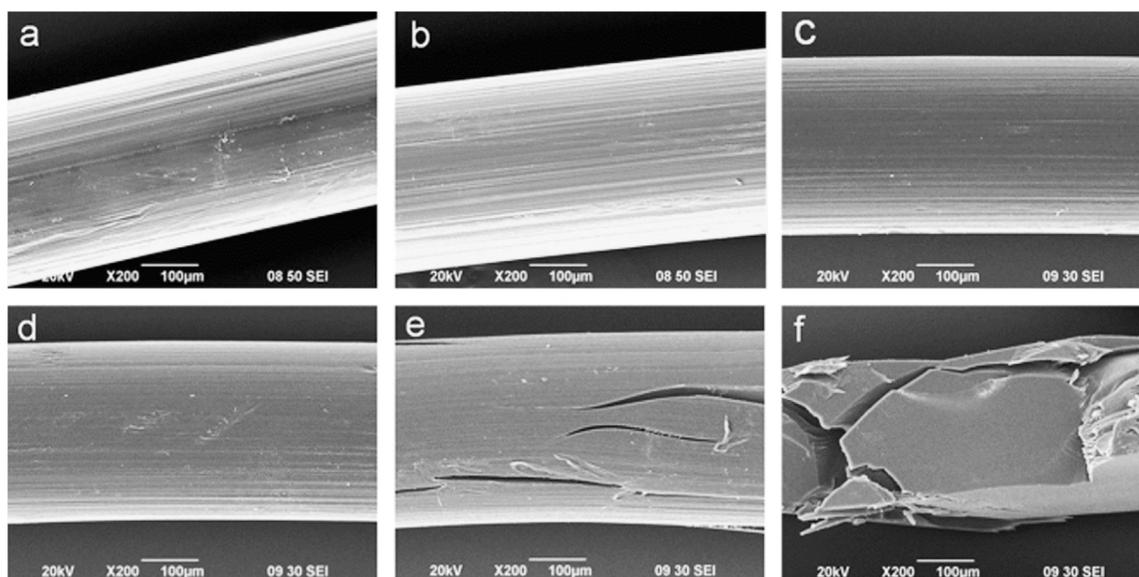

Fig. 2. The morphology changes of PDS stents in vitro degradation: where (a)–(f) photographs are stents degraded at 0, 2, 4, 8, 12, and 16 weeks. It was difficult to prepare PDS samples for SEM after 16 weeks, as the PDS materials were broken down into very small and fragile pieces after having vacuum dry [32].

the biocompatibility of magnesium alloys with the intestinal cells and tissues were evaluated. Mg tubes were investigated as connectors of intestine anastomosis as early as 1900s. Chlumský [33] successfully used of Mg connectors in humans and it took 2–4 weeks for complete breakdown, depending on the anatomical location and the size of the implant. Deng [34] found the average degradation rate of the AZ91D magnesium alloy in artificial intestinal juice was 0.33 mg/cm^2 day and it has good biocompatibility, no mutagenicity and no pyrogen reaction. Recent studies [35,36] indicated that the levels of apoptosis in intestinal epithelial cells (IEC-6) cultured in 100% Mg–6Zn alloy extracts were significantly higher than those in 60% and 20% extracts, and the IEC-6 cells displayed better cell functions in 20% extract of the Mg–6Zn alloy extracts, compared to the 100% or 60% extracts, which indicated the control of the corrosion rate is very essential. The biodegradable Mg–6Zn alloy samples are implanted around the cecum [37,38]. Results showed that magnesium–zinc alloy started to degrade at the third week (Fig. 3). Results of histological evaluation revealed that both the Mg–6Zn alloy and titanium (compared with the negative control) did not bring about organic damage to vital organs (Fig. 4). Superior to the Ti–3Al–2.5V alloy, the Mg–6Zn alloy enhanced the expression of transforming growth factor-β1 in healing tissue, and promoted the expression of both the vascular endothelial growth factor and the basic fibroblast growth factor, which helped angiogenesis and healing. The Mg–6Zn alloy reduced the expression of the tumor necrosis factor (TNF-α) at different stages and decreased inflammatory response, which may have been related to the zinc inhibiting TNF-α. In general, the Mg–6Zn alloy performed better than Ti–3Al–2.5V at promoting healing and reducing inflammation [38]. Cao et al. [39]

explored the safety and feasibility of biodegradable magnesium alloy stapler for gastrointestinal anastomosis in beagle dogs. There is no significant difference between the magnesium group and the control (titanium alloy) group, and the anastomosis was healed well with no dramatic inflammatory cell infiltration was observed. The degradation of magnesium alloy did not harm the important organs (liver, kidney, heart, brain and spleen).

4. Clinical trials of biodegradable intestinal stents

Dedicated intestinal stents are not available by far and there is currently no published clinical experience with intestinal stents of magnesium alloys. Fig. 5 shows three designs of biodegradable BD stents (ELLA-CS, Hradec Kralove, Czech Republic), which is originally designed for use in the treatment of esophageal stenosis. This BD stent has been successfully applied in the treatment of benign conditions in the lower gastrointestinal tract. The stents are manufactured from woven PDS monofilament. They are available with trunk diameters of 18–25 mm, typically with both ends flaring to 23–31 mm as shown in Fig. 5(a), and are in different lengths from 60 to 135 mm. Its degradation can be accelerated by a low ambient pH. The stent integrity and the radial force of the stent are maintained for 6–8 weeks following implantation and there is an extended period of dilation in comparison to conventional methods. Stent disintegration occurs 11–12 weeks following implantation and there is no need for removal. Flared ends reduced migration rates and radiopaque markers at both stent ends assist with accurate positioning [40]. The standard delivery system for esophageal implantation has an active length of 75 cm and can only be used for intestinal strictures
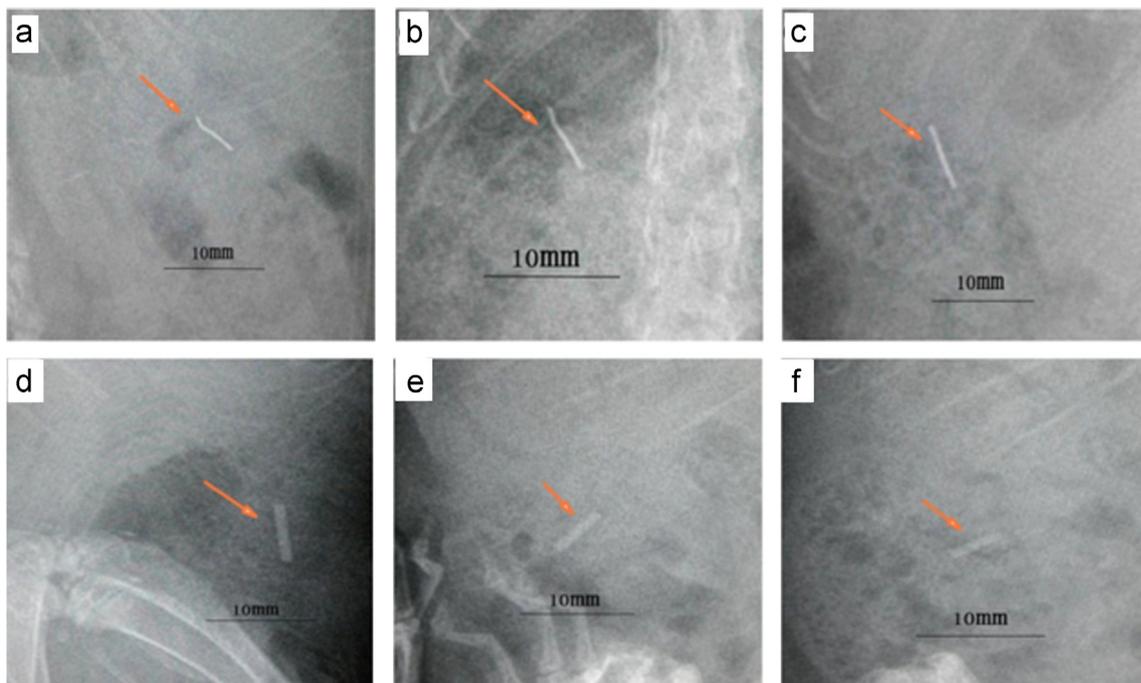

Fig. 3. X-ray films of cecum implanted titanium stick in a rat: (A) first week; (B) second week; (C) third week; Mg–6Zn alloy: (D) first week; (E) second week; (F) third week [37].
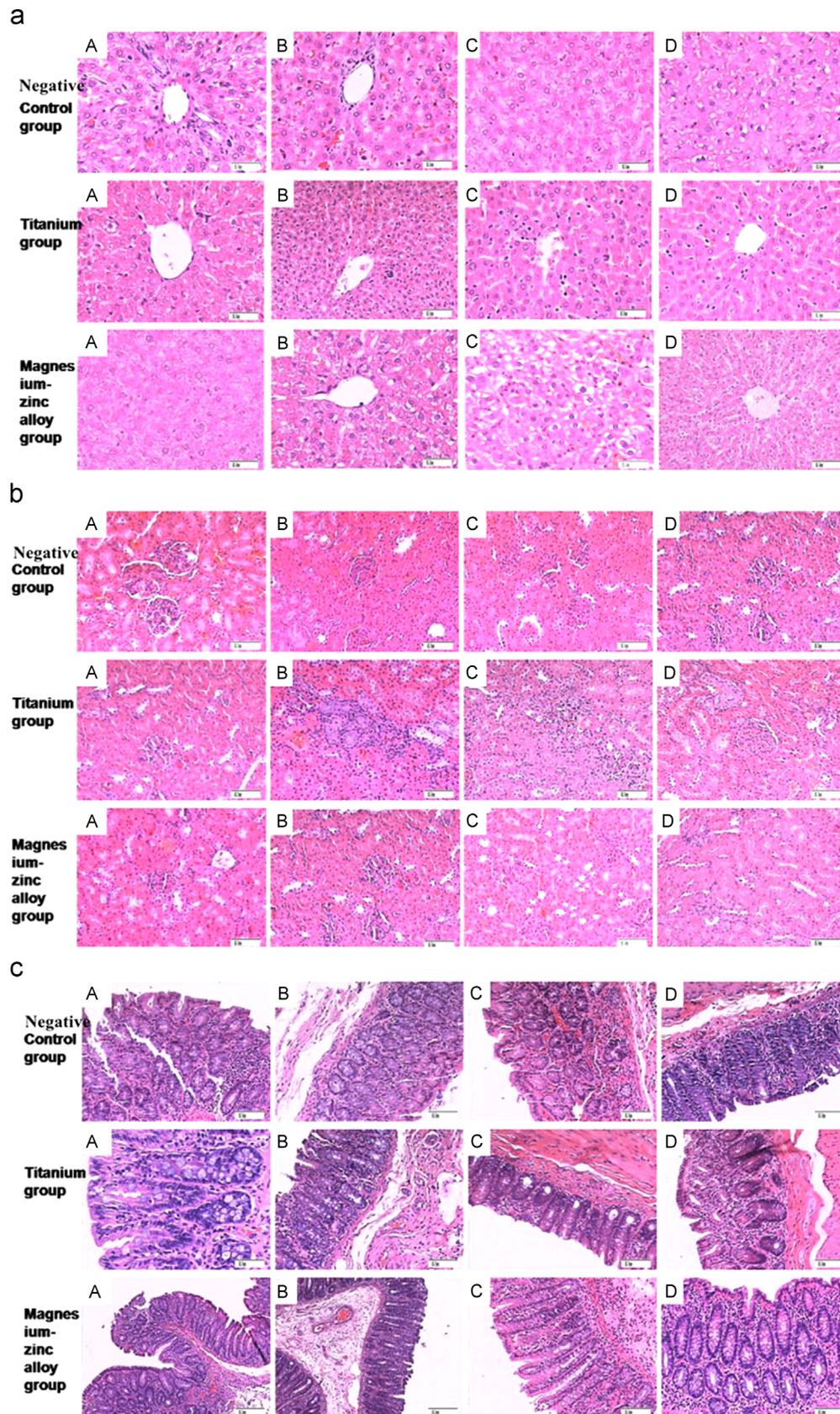
Fig. 4. Histological evaluation of (a) liver, (b) kidney, (c) cecum after implantation of titanium and Mg–6Zn stick into the cecum of a rat for (A) 1st week; (B) 2nd week; (C) 3rd week; and (D) 4th week (hematoxylin–eosin staining, 100 ×) [37].

up to the distal descending colon. Proximal stent insertion was accomplished by use of a custom made introducer inserted into an overtube after endoscope removal [41]. Up to now, BD stent is the only biodegradable stent that has been applied in the treatment of stricturing Crohn's disease [2,3,41], anastomotic colorectal strictures [31,42–44], and postsurgical colonic fistulas [44]. The cases and case series are summarized in Table 1.

4.1. Biodegradable stent for the treatment of benign stenoses in Crohn's disease

Strictures are a common complication of Crohn's disease, occurring in 1/3 of patients after 10 years of disease [41]. Rejchrt et al. [2] were the first who introduced this biodegradable stent for

the treatment of small and large intestinal stenoses in 2009. Insertion of biodegradable stents was successful in all three patients with tight benign intestinal stenoses as a complication of Crohn's disease. No stent migration or major complications were observed. In one case, two months after implantation, the stent was cutoff endoscopically and discharged spontaneously because the proximal flared end of the stent came into contact with the intestinal wall (without stent migration) and caused intermittent transit obstruction. A case series including 11 patients with stenosing Crohn's disease were reported in 2011 [3]. Biodegradable stent with three different designs were used, as shown in Fig. 3. Endoscopic insertion of the stents was successful at the first attempt in all patients except one. Endoscopic views of a typical stenosis before and after biodegradable stent insertion and corresponding fluoroscopic images are shown in Figs. 6 and 7, respectively. Subsequent follow-up was for
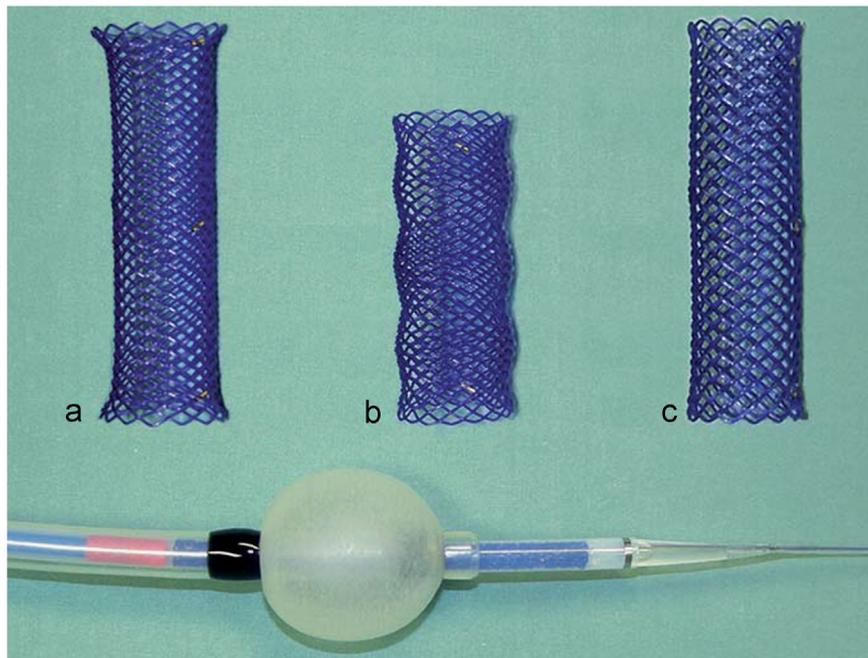

Fig. 5. Biodegradable BD stents (ELLA-CS, Hradec Kralove, Czech Republic) woven from polydioxanone filament with three different designs: design (a), flared at both ends; design (b) with a waved shape; and design (c) without flared ends. An introducer sheath loaded with a biodegradable stent and a balloon with a detachable olive is shown below [3].

Table 1
Cases series evaluating the outcomes of biodegradable stents for intestinal and colonic strictures.

Author	Year	Type of study	Indication	*n*	Outcome	Complications
Rejchrt et al. [2]	2009	CS	Stricturing CD	3	66% symptom-free end FU 33% Intermittent transit obstruction	0%
Rejchrt et al. [3]	2011	CS	Stricturing CD	11	Technical success rate 91% Symptom-free FU (12–27 weeks) 64% Time to stent degradation was 4 months	Stent migration, 27%
Rodrigues et al. [41]	2013	CR	Stricturing CD	1	Symptom-free end FU (16 months)	0%
Toth et al. [56]	2011	CR	PS	1	Symptom-free end FU (24 months)	hyperplastic tissue reaction
Janík et al. [42]	2011	CS	PS	3	Stoma reversal 66% Completely degradation after 4 months	0%
Belvedere et al. [57]	2012	CS	PS	1		0%
Repici et al. [31]	2013	CS	PS	11	45% symptom-free end FU (16 months)	Stent migration,, 36%
Pérez et al. [44]	2012	CS	PS and fistula	10	66% symptom-free end FU	Stent migration, 10%

CR: Case report; CS: Case series; CD: Crohn's disease; PS: Postsurgical strictures; FU: Follow-up.

a mean of 16 months, median 17 months, range 12–29 months. Stent migration was recorded in three patients. In two of them, waved stents, design (b) in Fig. 3, had been used, which indicated design (b) is defective. Results showed that mucosal overgrowth (epithelial hyperplasia) was not observed in any of the patients during the follow-up period. These were the only two reports of the use of biodegradable stents in the small bowel and proximal large bowel.

Rodrigues et al. [41] reported the case of a 33-year-old patient with long-standing Crohn's disease who developed a fibrotic stricture of the sigmoid too long to be amenable to balloon dilation. The use of a biodegradable polydioxanone stent was chosen to avoid surgery. The results showed that combined endoscopic and fluoroscopic placement of the stent was technically simple, safe and clinically successful, and no recurrence of obstructive symptoms occurred during a 16-month follow-up [41].
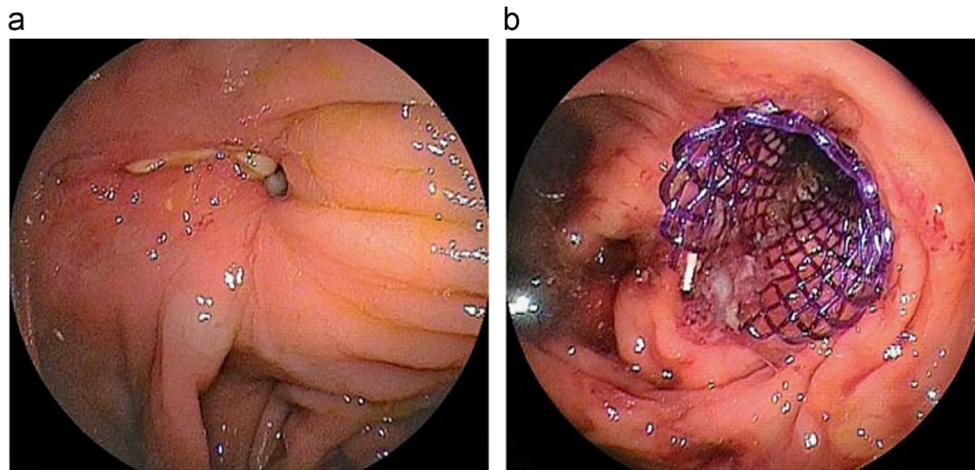

Fig. 6. Endoscopic views of a typical stenosis before and after biodegradable stent insertion. (a) An ileo-ascending colon anastomosis with a tight stenosis and ulcer. (b) A deployed biodegradable stent in the stenotic anastomosis immediately after its insertion [3].
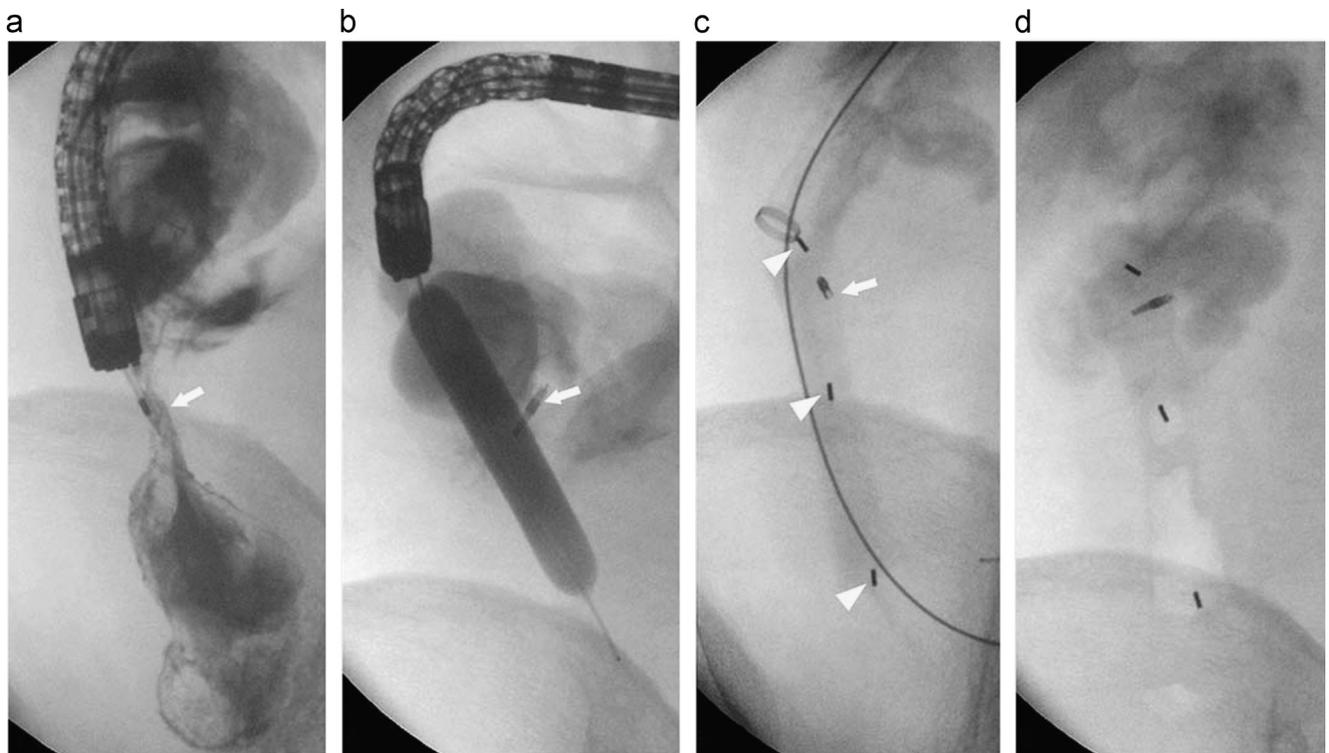

Fig. 7. Fluoroscopic images before and after biodegradable stent insertion from the same patient as shown in Fig. 6. (a) Stenosis (arrow) of the ileo-ascending colon anastomosis. (b) Balloon dilation of the stenotic area. The distal margin of the anastomosis is marked with a metallic clip (arrow). (c) Biodegradable stent, with three radio-opaque markers (arrowheads), in situ immediately after its deployment from the introducer. The distal margin of the stenosis is marked with a metallic clip (arrow). (d) Appearance of the biodegradable stent at the end of the procedure [3].

4.2. Biodegradable stent for the treatment of postsurgical colorectal strictures and fistulas

Strictures following colorectal surgery occur in 1.5–8% of patients [45]. Various factors are associated with the development of an anastomotic stricture like technical errors in confectioning the suture, poor blood supply, inflammation following small anastomotic leaks or radiotherapy [31]. Eleven patients (7 males, mean age 62.3 ± 8.5 years) with postsurgical benign strictures located within 20 cm from anal verge, refractory to mechanical or pneumatic dilation (at least 3 sessions) were treated with the BD stents [31]. Patients with concomitant presence of a fistula, the suspicion of malignancy, diverticular stenosis, previous stent placement, and a location of the stricture too close to the anus (< 5 cm) were deemed unfit for BD stenting. Results showed that technical success was achieved in all the patients. Stent migration was observed in four patients within the first 2 weeks after stent placement and was followed by recurrence of stricture and obstructive symptoms in all the cases. Among the seven patients who completed the process of stent biodegradation, five of them had complete resolution of the stricture and relief of symptoms. Two of 11 patients required surgical treatment during the follow-up period (mean 19.8 (range 42–15) months). The overall success rate of the BD stent was only 45% [31]. Endoscopic follow-up showed only a mild hyperplastic reaction, which resolved after stent degradation in the majority of patients. The authors considered the suboptimal efficacy of the BD stent is related more with the early migration rather than to an intrinsic failure in dilating the stricture. There are three factors that contribute to the early migration: the nondedicated design of the stent (stents for colonic strictures require a larger caliber than esophageal stents), the predilatation and passage of stools, and the laxative use. Dedicated stents with large diameter and antimigration findings could potentially improve the outcome of patients with refractory benign colorectal strictures [31]. Stent migration was not observed in other reports which included limited number of patients. Toth et al. [43] reported a case with a benign stricture in a colorectal anastomosis, treated with a biodegradable stent. The stent position was monitored 6 weeks after deployment and shown to be partially reabsorbed. The patient was still asymptomatic and a colonoscopy revealed complete biodegradation of the stent 5 months later. However, a hyperplastic tissue reaction was observed at distal part of the colorectal stricture. At this time, the lumen had reduced to 8 mm and was therefore dilated up to 18 mm. A follow-up was performed 2 years later, which revealed that the patient had no clinical symptoms although the size of the lumen had reduced [43]. In another study, biodegradable stents were inserted into three male patients (median age 66) who developed benign strictures after radiotherapy and resection of a recto-sigmoid carcinoma [42]. The results showed that all stents were placed successfully without complications after pre-dilatation to 20 mm under fluoroscopic guidance. Stent degradation occurred in all patients 4–5 months following implantation, and long-term anastomotic patency was demonstrated in all [42]. This allowed reversal of the colostomy and physiological defecation in two patients. Reversal was not undertaken in one due to subsequent development of liver metastases. No stent migration or occlusion occurred [42]. It was concluded that biodegradable stents can maintain an adequate lumen across anastomotic strictures resistant to balloon dilatation. They seem to allow stricture re-modeling resulting in maintained dilatation after degradation [42].

In 2012, one study was performed to evaluate the safety of biodegradable stents for the treatment of colonic strictures and fistulas [44]. They analyzed the results from 10 patients with either a postsurgical colorectal stricture ($n=7$) or rectocutaneous fistula ($n=3$) treated with the biodegradable SX-ELLA esophageal stent [44]. In the patients with rectocutaneous fistulas ($n=2$), suture dehiscence ($n=1$), and postsurgical cloaca with stricture ($n=1$), the covered stents that had a polyethylene internal coating were used. The results showed that stents were successfully placed in nine patients, although early migration subsequently occurred in one. Placement was impossible in one patient due to deformity of the area and the fact that the stricture was approximately 30 cm from the anus. The fistulas were successfully closed in all patients, although symptoms reappeared in one patient. Breakage of the polyethylene coating occurred in one of the coating stents. In the six patients who received stents for strictures, symptoms resolved in five; in the remaining patient, the stent migrated shortly after the endoscopy [44]. It was concluded that treatment of colonic strictures and rectocutaneous fistulas with biodegradable stents is an effective alternative in the short-to-medium term. The stent does not have to be removed and is subject to very few complications [44].

The above cases indicated that the technical success of BD stent in intestinal insertion is high, except for proximal stenoses and in patients with considerable deformity and angulations. Early stent migration rate is about 20%, which is the main reason of clinical failure. The early migration can be solved using cyanoacrylate, with a clip placement in the upper flare or by improvements in stent design. Severe mucosal hyperplastic reaction resulting in obstruction after biodegradable stenting has been documented in esophageal strictures [46,47] but not in intestinal strictures thus far.

5. Concluding remarks

Biodegradable stents overcome some of the problems encountered with self-expanding metal stents. The primary advantage of biodegradable stents over self-expandable metallic stents is that removal is not required. Biodegradable polymer stents has been successfully employed in the treatment of benign esophageal strictures [5,48–50], malignant esophageal strictures [51], and esophageal perforation or anastomotic leak [52]. There are, however, limited data available on their use in the intestinal tract. The clinical experience with currently the only biodegradable stents (BD stents) for endoscopic placement, made of poly-dioxanone, have shown promising results. Intestinal stents with improved design and reduced migration are expected. Clinical trials

including larger number of patients and longer follow-ups will be necessary. The price of these nowadays is also an important limitation [8].

Compared to biodegradable polymer, the development of biodegradable magnesium alloys is still in its infancy. Nevertheless, besides cardiovascular stents and orthopedic implants, preliminary attempts of biodegradable Mg-based devices have been made in many areas such as esophageal stent for infants [53], biliary stents [54] and ureteral stents [55]. With many of the key fundamental and practical issues resolved and better methods for adjusting corrosion resistance and progressing biocompatibilies of magnesium alloys, it is possible to use biodegradable intestinal stents made of magnesium alloys in hospital in the not too distant future.

Acknowledgments

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