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# Silicone-covered biodegradable magnesium-stent insertion in the esophagus: a comparison with plastic stents

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***Abstract***

**Background:** We determined the feasibility of, and tissue response to silicone-covered biodegradable magnesium- and plastic-stent insertion into the esophagus in rabbits.

**Methods:** The mechanical compression–recovery characteristics and degradation behaviors of the magnesium stent were investigated *in vitro*. A total of 45 rabbits were randomly divided into a magnesium- ($n$ = 15) and a plastic- ($n$ = 15) stent group, and underwent stent insertion into the lower third of the esophagus under fluoroscopic guidance; a control group ($n$ = 15) did not undergo the intervention. Esophagography was performed at 1, 2, and 4 weeks. Five rabbits in each group were euthanized at each time point for histological examination.

**Results:** Silicone-covered magnesium stents showed similar radial force to plastic stents ($p > 0.05$). The magnesium stents degraded rapidly in an acidic solution, but 90.2% ± 3.1% of the residual mass was maintained after a 2-week degradation in a solution with a pH of 4.0. All stent insertions were well tolerated. Magnesium stents migrated in six rabbits (one at 1 week, one at 2 weeks and four at 4 weeks), and plastic stents migrated in three rabbits (one at 2 weeks and two at 4 weeks; $p > 0.05$). Esophageal wall remodeling (thinner epithelial and smooth muscle layers) was similar in both stented groups ($p > 0.05$), and the esophagus wall was found to be significantly thinner in the stented groups than in the control group ($p < 0.05$). Esophageal injury and collagen deposition following stent insertion were similar and did not differ from the control group ($p > 0.05$).

**Conclusions:** Esophageal silicone-covered magnesium stents provided reliable support for at least 2 weeks, with acceptable migration rates and without causing severe injury or tissue reaction compared with plastic stents.

***Keywords:*** biodegradable stent, esophagus, magnesium, tissue reaction

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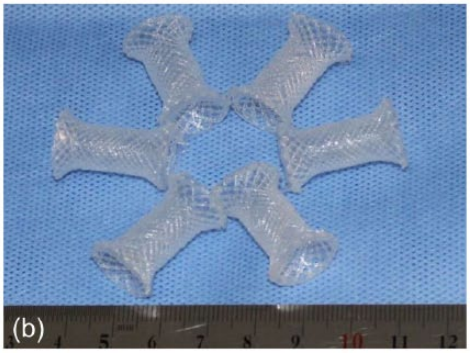
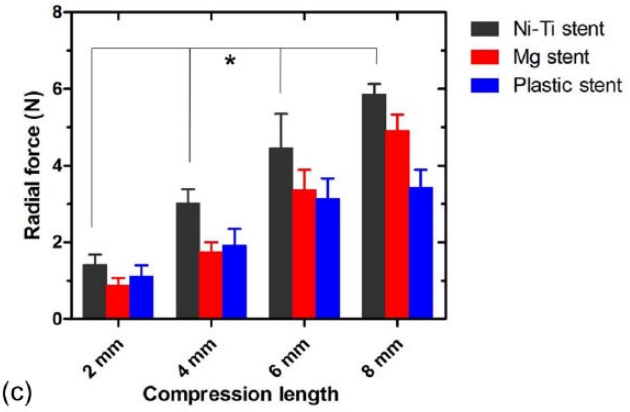
## Introduction

Benign stricture of the esophagus (BSE) can severely reduce quality of life and cause major complications such as aspiration, weight loss, and malnutrition [Ferguson, 2005].

Endoscopic or fluoroscopic dilatation of the esophagus with balloons or graduated dilators has become the treatment of choice for BSE. However, this treatment remains controversial since long-term recurrence rates progressively increase with time, contingent upon stricture etiology, from 20% to 61% [Choi *et al.* 2007; Cheng *et al.* 2003]. Permanent placement of metallic stents is not recommended for BSE as the procedure is associated with additional problems such as re-stricture from tissue hyperplasia, stent migration, and fistula formation [Schembre *et al.* 2011; Bick *et al.* 2013; Stewart *et al.* 2013]. Although the use of a fully covered membrane makes a metallic stent removable and theoretically can reduce long-term complications, this design runs the risk of in-stent tissue growth during insertion or dysphagia recurrence after removal [Hirdes *et al.* 2012; Vlavianos and Zabron, 2012]. Self-expandable plastic stents minimize tissue reaction and can be removed


| Compression length | Radial force (N) | | |
|---|---|---|---|
| | Ni-Ti | Mg | PP |
| 2 mm | 1.42± 0.26 | 0.89 ± 0.18 | 1.12± 0.28 |
| 4 mm | 3.02± 0.37 | 1.75 ± 0.25 | 1.92± 0.43 |
| 6 mm | 4.46± 0.89 | 3.38 ± 0.51 | 3.14± 0.53 |
| 8 mm | 5.86± 0.27 | 4.91 ± 0.42 | 3.43± 0.46 |

**Figure 1.** Photographs of the magnesium (a) and plastic (b) stents. Mechanical analysis revealed that the magnesium stent had a similar radial force to the plastic stent ($p > 0.05$) (c).

easily, and were thus recommended for BSE treatment.

However, due to their nonbiodegradable character, the stent-retrieval procedure exposes patients to the risk of bleeding and pain [Ham and Kim, 2014; Yim, 2014]. Biodegradable, silicone-covered magnesium esophageal stents are very appealing as they would provide similar radial support as other metallic stents, without causing complications associated with nonbiodegradable stent insertion.

We inserted biodegradable, silicone-covered magnesium stents into the normal esophagus of rabbits to determine the feasibility of this technique and observe the *in vivo* tissue reaction after stent insertion in comparison with that after plastic stent insertion. In addition, the mechanical support provided and the biodegradation process were tested *in vitro*.

## Materials and methods

### *Silicone-covered magnesium and plastic stents*

The silicone-covered magnesium and plastic stents used consisted of two parts: a bare stent and a silicone membrane. The bare magnesium stent was knitted from a 0.20 mm-wide magnesium alloy wire (AZ31, Mg-3Al-1Zn). AZ31 is a commercial magnesium alloy (Sanming, Biomedical Company, Yangzhou, China) with the following chemical composition (in mass percentage): 3% Al, 1% Zn, and 0.43% Mn and Mg (balance). It is supplied in the form of cast ingots. The plastic stent is knitted from a 0.25 mm diameter polypropylene wire (density, 76 g/m$^2$) (Convidien, Trevoux, France). The density of wire cross distribution, the height, and the knit angle of the stent were the same as those of the magnesium stent made using the same cast ingots. The stent consisted of a cylindrical, cross-linked mesh body made of the magnesium alloy or polypropylene, with a 14 mm cylinder and a dilated portion at its head and distal end to prevent stent migration. The diameter of the main body was 10 mm; the total stent length was 31 mm when fully expanded (Figure 1a and b). A silicone membrane (C6-530 with A and B components, Dow Corning Company, China) was used to coat the stent body *via* a dipping and spinning method: (a) precision aluminum molds of the stent were used to fabricate the wire framework; (b) equal portions of the two parts of the silicone rubber were thoroughly blended together using *N*-octane as a solvent prior to use; (c) the mixed silicone was dipped on the stent mold and cured for 6 h at

80°C for drying. The molds were cooled for 3 h in ambient conditions; the stent prototypes were stripped from the molds. The stent body was not radio-opaque, so a mark was placed at its distal end to facilitate accurate positioning under fluoroscopy. We compressed and deployed each stent using a 6 mm-wide (approximately 18F) delivery system.

### *Magnesium-silicone stent evaluation* in vitro

The compression–recovery characteristics of the silicone-covered magnesium stent and plastic stent were investigated using a mechanical testing machine (Instron 5567, Norwood, MA, USA). Magnesium-stent degradation was evaluated by determining the mass lost from the stent. Stents were sectioned into $1 \times 1$ mm$^2$ squares. The preweighed pieces were incubated at 37°C in 20.0 ml of two phosphate-buffered saline (PBS) solutions with pH values of 7.4 and 4.0. At each experimental time point, triplicate stent samples were recovered and rinsed with distilled water; the stents were dried to a constant weight in vacuum desiccators. Mass loss was determined gravimetrically by comparing the dry weight remaining at a specific time with the initial weight.

### *Stent insertion*

All protocols were approved by the Animal Research Committee of our institution and conducted in accordance with the guidelines of the International Council on Animal Care. A total of 45 healthy rabbits of both sexes (weight, 2.3–3.8 kg) were randomly divided into a magnesium-stent group ($n$ = 15), a plastic-stent group ($n$ = 15), and a control group ($n$ = 15). Rabbits in the magnesium- and plastic-stent groups underwent stent placement in the lower third of the esophagus. A 0.035-inch, 260 cm-long, stiff exchange wire (Terumo, Tokyo, Japan) was inserted through the mouth and into the stomach under fluoroscopic guidance. The stent-delivery system was introduced over the guidewire until it reached the lower third of the esophagus. The stent was then released, according to esophagography images obtained under fluoroscopic guidance. A balloon catheter ($10 \times 40$ mm) was inflated within the stent to achieve full stent expansion. Repeat esophagography was performed to confirm the degree of stent expansion and exclude esophageal perforation. Animals in the control group did not undergo stent insertion.

### *Follow up*

Esophagography was performed under general anesthesia and in the upright position prior to stent placement, and at 1, 2, and 4 weeks following stent insertion. Stent migration, stent patency, and diameter of the stented esophagus were compared between the two groups.

### *Histological examination*

Five animals in each group were euthanized at each time point to compare tissue reactions. The inserted stent was carefully removed from the resected esophageal sample. The silicone-covered magnesium stent was knitted using a magnesium line and comprised 420 mesh cells. Considering that the support provided by the stent was mainly attributable to the mesh cells, the stent-degradation rate was determined by calculating the percentage of degraded mesh cells. A mesh cell was considered to be degraded if one of its four sides appeared discontinuous under microscopic observation. Minor, moderate, and severe degradation of the magnesium-silicone stent were defined as $< 25\%$, 25–50%, and $> 50\%$ broken mesh cells in the total number of mesh cells.

The stented and control esophageal samples were fixed in 10% neutral-buffered formalin for a minimum of 48 h, passed through a series of graded ethanol solutions (70–100%), and embedded in paraffin. Serial paraffin-embedded, esophageal cross-sections were stained with hematoxylin and eosin (HE) to evaluate the inflammatory reaction based on revised inflammation scores [Kornowski *et al*. 1998]. The scoring was performed as follows: 0 = no submucosal inflammatory cell infiltration; 1 = inflammatory cells infiltrating less than one third of the submucosa; 2 = inflammatory cells infiltrating more than one third but not the entire submucosa; and 3 = inflammatory cells infiltrating the entire submucosa. Masson trichrome staining was used to assess submucosal collagen deposition. Esophageal samples were immunostained with mouse anti-proliferating cell nuclear antigen (PCNA) antibody (1:100 dilution) (NeoMarkers, Thermo Fisher Scientific Inc., Fremont, CA, USA) and mouse monoclonal α-smooth muscle actin (α-SMA) antibody (1:50 dilution) (Santa Cruz Biotechnology Inc., CA, USA) *via* the Elivision immunohistochemical technique. Negative controls were prepared by omitting the primary antibodies. The pathologist who reviewed the specimens and performed the

analysis was blinded to the animal randomization, treatment procedures, and follow-up protocols.

### Statistical analysis

GraphPad Prism 5.0 software (GraphPad Software Inc., San Diego, CA, USA) was used for statistical analysis. Fisher's exact test was used to compare nonparametric data. Continuous variables were expressed as mean ± standard deviation, and categorical variables as numbers or percentages. One-way and two-way analysis of variance (ANOVA) was used to compare the overall changes in esophageal diameter following stent insertion and at each follow-up time point, and to compare the PCNA proliferation index and collagen area at each follow-up time point within or between the control and stented groups. Before one-way ANOVA, the homogeneity of variance and normal distribution of the dependent variables were assessed using the Shapiro–Wilk test. Statistical significance was defined as $p < 0.05$.

## Results

### Magnesium-silicone stent and its mechanical evaluation

The silicone membrane had a uniform thickness of 100 μm, it was tightly wrapped and fixed to the cross-linked, knitted, bare magnesium or plastic mesh tube and maintained its size and morphology due to its excellent flexibility and elasticity. The silicone-covered magnesium stent displayed good elastic deformation properties owing to its ability to spring back after compression, with no silicone membrane tearing or ablations after 46 repeated compressions (compression distance: 0–8 mm). The magnesium stent showed a radial force of 0.89 ± 0.18, 1.75 ± 0.25, 3.38 ± 0.51, and 4.91 ± 0.42 N when compressed by 2, 4, 6, and 8 mm, respectively, which was similar to that for the plastic stent ($p > 0.05$) at the same compression displacement (Figure 1c). Thus, the silicone-coated magnesium stents possessed good flexibility and elasticity, and could provide enough support against lesion compression when used *in vivo*.

### Biodegradation of magnesium-silicone stent in vitro

The degradation behaviors of the magnesium-silicone stents in terms of the magnesium mass lost were determined in buffer solutions with pH values of 7.4 and 4.0 (Figure 2). The residual mass of the silicone-coated wires was 96.3% ± 2.4%, 90.2% ± 3.1%, and 73.4% ± 4.7% in acidic PBS (pH 4.0) compared with 98.4% ± 1.1%, 92.5% ± 2.8%, and 80.7% ± 4.3% in neutral PBS (pH 7.4), at 1, 2, and 4 weeks, respectively ($p < 0.01$). However, despite a faster speed of degradation in acidic solution, the silicone-coated wires maintained 73.4% of their mass weight at 4 weeks, indicating that silicone-coated magnesium was a reasonable choice of material for the fabrication of biodegradable stents in terms of possible retention time.

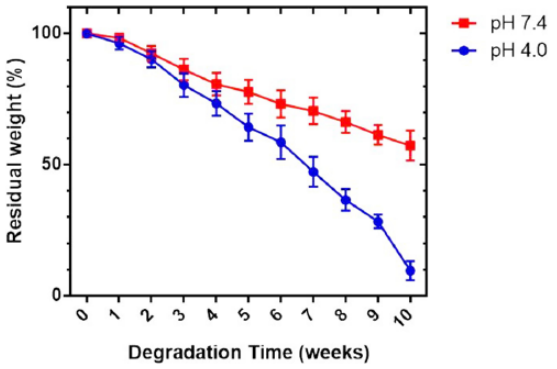



**Figure 2.** Analysis of the degradation of the silicone-covered magnesium stent samples in phosphate-buffered saline with pH values of 7.4 and 4.0.

### Intervention procedure

Stenting was successful in all 30 rabbits using magnesium and plastic stents. All rabbits tolerated the procedure well. Procedure-related adverse events, including esophageal perforation and bleeding, did not occur during or following stent insertion. Esophagography revealed that the contrast agent passed smoothly through the stented esophagus in both groups (Figure 3a and b). No immediate stent migration into the stomach occurred after stent placement.

### Follow up

All rabbits in both groups underwent regular esophagography; no animal died during follow up. Stent migration occurred in six rabbits in the magnesium-stent group (1 week, one rabbit; 2 weeks, one rabbit; and 4 weeks, four rabbits), and the plastic stent migrated in three rabbits (one at 2 weeks and two at 4 weeks; $p > 0.05$). The

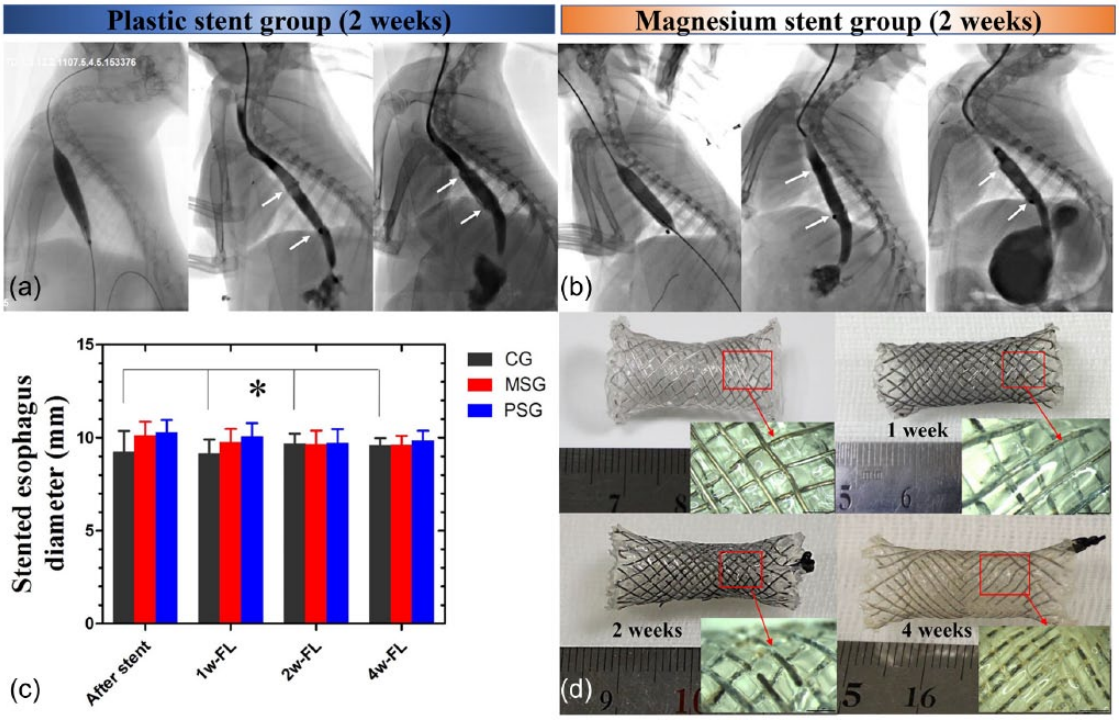



**Figure 3.** Esophagography during, immediately after, and 2 weeks after magnesium (a) and plastic (b) stent insertion revealed that the stented esophagus is patent. The diameter of the stented esophagus immediately after stent insertion and after 1, 2, and 4 weeks follow up in the control, magnesium- stent, and plastic-stent groups (c). Macro- and microscopic examination of the magnesium stent showed an increase in the number of biodegraded mesh cells with time (d). *$p < 0.05$ for comparisons of the control and stented groups. CG, control group; MSG, magnesium-stent group; PSG, plastic-stent group.

esophageal diameter in the magnesium-stent group was 10.10 ± 0.75 mm after stent insertion and 9.73 ± 0.73 mm after 1 week, which were larger than the corresponding values in the control group (9.21 ± 1.14 mm and 9.12 ± 0.78 mm, respectively; $p < 0.05$). Follow-up esophagography revealed no in-stent stenosis. The mean diameter of the magnesium-stented esophagus (9.59 ± 0.51 mm) at the end of follow up (4 weeks) was similar to that observed immediately after stent insertion (10.10 ± 0.75 mm; $p > 0.05$), and that in the control group at 4 weeks (9.55 ± 0.41 mm; $p > 0.05$). The esophageal diameter did not significantly differ between the magnesium- and plastic-stent groups immediately after stent insertion and at each follow-up time point ($p > 0.05$) (Figure 3b).

### *The magnesium-stent morphological changes* in vivo

Microscopic examination of the magnesium-silicone stents revealed that biodegraded mesh cells accounted for 5.1% ± 2.5% ($n = 4$; minor degradation) of the total cells at 1 week, 16.3% ± 3.6% ($n = 4$; minor degradation) at 2 weeks, and 89.0% ($n = 1$; severe degradation) at 4 weeks. The degradation rates significantly differed between 1 week and 2 weeks ($p = 0.002$) (Figure 3d). Interestingly, among the six magnesium-silicone stents that migrated into the stomach, four were almost completely degraded, with only 1.5% ± 2.3% nondegraded mesh cells (severe degradation), and the remaining two stents were eliminated from the body.

### *Histological study*

HE staining revealed significant esophageal wall remodeling in the magnesium- and plastic-stent groups than in the control group. The inflammation scores at 1, 2, and 4 weeks (0.2 ± 0.4, 0.4 ± 0.5, and 0.2 ± 0.4, respectively) in the magnesium-stent group were similar to those in the plastic-stent and control group ($p > 0.05$). PCNA-positive cells (squamous epithelial cells)

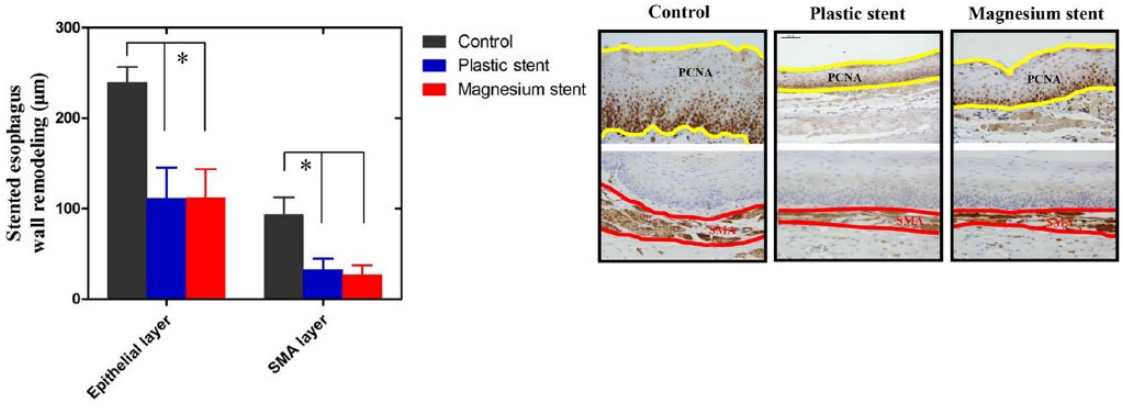



**Figure 4.** Both the epithelial (proliferating cell nuclear antigen-positive cells) and smooth muscle cell layers were significantly thinner in the magnesium- and plastic-stent groups than in the control group (magnification ×400; the yellow and red lines indicate the thickness of the epithelial and smooth muscle actin [SMA] layers, respectively). *$p < 0.05$ for comparisons between the control and the stented groups.

were mainly found in the epithelial layer; squamous epithelial cells located near the lumen and close to the stent were mostly negative for PCNA. Quantitative analysis of the PCNA-positive cells revealed no significant difference in proliferation index between the two stented groups and the control ($p > 0.05$). The epithelial layer, as measured on PCNA staining, was much thinner in the magnesium- (111.4 ± 32.5 μm) and plastic- (111.30 ± 34.08 μm) stent groups than in the control group (239.5 ± 17.2 μm; $p < 0.05$). Immunostaining revealed that the SMA layer in the media was significantly thinner in the magnesium- (27.0 ± 10.3 μm) and plastic- (32.42 ± 12.14 μm) stent groups than in the control (93.6 ± 19.0 μm; $p < 0.05$). However, the thickness of the epithelial and SMA layers did not differ between the two stented groups and at different follow-up time points ($p > 0.05$). Masson staining revealed that collagen was mainly localized in the submucosa, with no significant differences between the stented groups and the control group at each follow-up time point ($p > 0.05$), indicating that the tissue reaction to injury caused by stent dilation and degradation was similar to that in the control group (Figure 4).

## Discussion

We determined the feasibility of, and tissue response to biodegradable magnesium-stent insertion into the normal esophagus of rabbits. Our main findings are as follows. (a) Silicone-covered magnesium stents provided reliable radial force comparable with plastic stents. (b) The procedural success rate of magnesium-stent insertion was 100%, with the stents providing good support for at least 2 weeks before undergoing rapid biodegradation *in vivo*. (c) Stenting effectively resulted in esophageal wall remodeling, which was associated with minimal injury and inflammatory reaction. BSE, including refractory peptic, caustic, anastomotic, and post-radiotherapy strictures, may cause difficulty in feeding and greatly affect quality of life [Ferguson, 2005].

Esophageal stent insertion can effectively recanalize the occluded lumen without open surgery and is widely used to treat malignant esophageal obstruction [Na *et al.* 2013]. However, since long-term or permanent stent insertion is associated with stent migration, esophageal perforation, fistula, and even hemorrhage, it cannot be used to treat BSE. We had previously developed a retrievable, temporary stent and a temporary, drug-eluting stent to treat benign cardia strictures, with good treatment outcomes. However, the insertion of these stents was nevertheless associated with complications during stent retrieval and stent migration into the stomach. Ideally, stents for BSE should provide enough force to tear the stricture and then completely biodegrade to reduce complications caused by stent placement, without precluding repeated stent insertion. The magnesium alloy we employed is rigid and undergoes *in vivo* degradation [Gu *et al.* 2009].

This prevents a postimplantation inflammatory response and tissue proliferation, and thus, the

alloy is ideal for *in vivo* stents [Li *et al.* 2015]. However, this magnesium alloy undergoes rapid degradation (nearly 50% degradation after 1 week *in vitro*). Rapid degradation can lead to rapid loss of the mechanical properties of the alloy, making it difficult to maintain long-term structural support after implantation to effectively treat the disease [Wong *et al.* 2010]. Silicone has excellent elasticity, coating properties, and is resistant to *in vivo* degradation. In this study, magnesium alloy wires were used as rigid stent struts, and silicone membranes were used to cover the magnesium struts. The main advantages of this design included: (a) stabilization of the magnesium alloy stent structure; (b) bonding of the wire crossing points; (c) improvement of repeated radial expansibility and contractibility; (d) isolation of the magnesium alloy, preventing it from coming into direct contact with bodily fluids and increasing biodegradation time; (e) maintenance of stent structure during degradation of the magnesium alloy; (f) excretion of the silicone membrane through the stool after stent degradation.

Mechanical tests showed that under different compression distances, this stent has excellent recovery properties. After nearly 50 compressions, the material could still maintain its original mechanical compressive strength. This illustrates that the silicone-stabilized magnesium alloy tubular stent can maintain its mechanical properties and structural stability.

Stent degradation rate directly affects the structural support provided by the stent. *In vitro* experiments revealed that the silicone coating increased the degradation time of the magnesium alloy. In neutral PBS, 60% of the original mass remained after 10 weeks, while in acidic PBS, complete degradation occurred within 10 weeks. *In vivo* examination revealed that only 5.1% and 16.3% of the inserted magnesium-silicone mesh had biodegraded at 1 and 2 weeks of follow up, respectively, indicating that the stent provided good support up to 2 weeks in the rabbit esophagus. The magnesium-silicone stent rapidly biodegraded, lost radial force and collapsed after 2 weeks. All the above data indicate that magnesium-silicone stents effectively provided good support for at least 2 weeks.

Thrombus formation and distal embolism are major problems with magnesium stents inserted in the coronary artery [Haude *et al.* 2013]. However, in our study, the degraded stents, including the nonbiodegradable silicone, were safely excreted from the body. Two magnesium-silicone stents that migrated into the stomach when their mechanical support was lost were confirmed to have been safely excreted from the body before 4 weeks.

The basic concept underlying the treatment of BSEs is to tear the fibrous connective tissue or hyperplastic smooth muscle layer, and provide enough support until the esophageal wall has healed. Our previous work has indicated that the optimal duration of stenting for cardia strictures is 2–4 weeks [Zhu *et al.* 2011, 2013a, 2013b]. Tanaka and colleagues reported the use of a polylactic stent for the treatment of benign gastrointestinal tract stenosis, and this ultraflex-type stent made from machine-knitted polylactic acid monofilaments showed better radial force than a metallic wall stent. However, this stent was difficult to compress into a delivery system, and its migration rate was 100% at 12–14 days after insertion [Tanaka *et al.* 2006]. Although the effective support time for the magnesium-silicone stent was only 2 weeks, we believe that it may still yield good treatment outcomes in BSE, mainly because on pathological examination, we found that the epithelial and SMA layers had already stretched and become much thinner at 1 and 2 weeks, indicating the remodeling process had been completed. Moreover, our previous studies were mainly focused on cardia strictures, which often require greater dilation for longer durations than esophageal strictures [Ferguson, 2005; Na *et al.* 2013; Zhu *et al.* 2011, 2013a, 2013b]. The other pathological findings, including inflammation scores on HE staining and esophageal wall injury assessed using PCNA staining of the epithelial layer and submucosal collagen deposition, revealed that magnesium-stent insertion or biodegradation itself did not cause severe damage to the esophageal wall, induce significant inflammatory reaction, or result in scar formation. In this study, we consider that the rabbit was suitable as a model of the human esophagus as it has similar esophageal wall structure and gastric pH conditions to humans. The muscle layer transitions from striated muscle in the upper esophagus to smooth muscle in the lower esophagus. The gastric pH during the digestion of food material is maintained between 1 and 2. Both these properties are similar to those observed in humans [Davies *et al.* 2003]. However, the entire

esophagus and the first half of the stomach are covered by squamous epithelium, which is different to the case in humans.

This study has some limitations. (a) The magnesium-silicone stent was inserted into a normal rabbit esophagus; the tissue reaction in the normal esophagus may differ from that in an esophageal stricture. (b) Effective support was provided for only 2 weeks; further research is required to delay biodegradation and improve the duration of support. (c) This stent should be applied in a BSE model to investigate fully its feasibility, efficacy, and tissue reaction *in vivo*.

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Yue-Qi Zhu and Kai Yang contributed equally to this study.

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## Conflict of interest statement

The authors declare that there is no conflict of interest.

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