Current status and future trends of biodegradable stents for esophageal stenosis: A literature review

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To the Editor: Esophageal stenosis can be either benign or malignant. Benign stenosis usually results from esophageal reflux, radiation therapy, corrosive ingestion, or surgical anastomosis following endoscopic submucosal dissection (ESD) or endoscopic mucosal resection for early esophageal tumors. Malignant stenosis is caused by advanced cancer. Esophageal stenosis often leads to dysphagia, malnutrition, aspiration, and respiratory failure, making conservative treatment challenging. Stent insertion is a primary option for relieving dysphagia, managing stenosis-related complications, and improving patient quality of life.

Esophageal stent designs have evolved from rigid plastic tubes to flexible self-expanding metal stents (SEMSs) and self-expanding plastic stents (SEPSs). SEMSs can be either partially or fully covered. Partially covered SEMSs can be firmly anchored to the esophageal wall to prevent stent migration but often lead to restenosis and difficult removal due to mucosal hyperplasia. Fully covered SEMSs and SEPSs reduce tissue reactive hyperplasia but have higher migration rates, reducing treatment effectiveness and potentially causing other serious complications. Additionally, repeated endoscopic procedures are often needed, increasing physical and psychological pain and financial burdens for patients. Overall, these stents exhibit certain limitations. Ideally, esophageal stents should disappear once their purpose is met, leading to the development of biodegradable stents (BDSs). This article aims to clarify the current research status of different materials in biodegradable esophageal stent development, highlight the strengths and limitations of existing BDSs, and provide insights into future development directions.

Degradable polymers are leading the development of biodegradable esophageal stents. Synthetic polymers offer reliable material sources without immunogenic concerns and can be chemically tailored for precise structures and high processing flexibility. They degrade into carbon dioxide and water in the body and are excreted through respiration and urine, posing no health risks. Since the 1960s, the US Food and Drug Administration (FDA) has approved numerous synthetic biodegradable polymers, such as poly (lactic acid) (PLA), poly (glycolic acid) (PGA), poly (lactic-co-glycolic acid) (PLGA), poly (caprolactone) (PCL), and polydioxanone (PDO). These materials are widely used to manufacture biodegradable sutures, medical implants, tissue engineering stents, drug delivery systems, and medical esthetic products.

In 1996, the clinical use of the poly-L-lactide (PLLA) esophageal stent was first reported, but it was poorly effective, with issues of stent collapse and recurrent dysphagia. In 2006, Tanaka *et al*[1] introduced an improved PLLA stent (Marui Textile Machinery Co., Ltd., Osaka, Japan). This stent was used for treating benign esophageal stenosis, and no restenosis was observed at follow-up times of 7–24 months. However, the high early stent migration rate (77%) limited its wider clinical application. The SX ELLA-BDS (Ella-CS, Hradec Králové, Czech Republic), made from PDO, is the only Conformité Européenne (CE) marked biodegradable esophageal stent for treating refractory benign esophageal stenosis (RBES) and was approved for the European market in 2007. Clinical studies have shown that ELLA-BDS is effective in treating benign esophageal stenosis. However, most patients in these studies experienced stenosis recurrence and dysphagia symptoms within 6 months. Thus, single-use BDS only provides short-term benefits, and the sequential placement of BDS has emerged as a suggested solution to avoid the need for continuous dilation. For malignant esophageal stenosis, some studies have shown that concurrent single-dose brachytherapy and BDS placement are technically feasible and improve patient dysphagia. However, there is a high incidence of complications, including severe retrosternal pain, nausea and vomiting, hematemesis, and recurrent dysphagia, preventing a

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normal diet in most patients. In some studies, however, the ELLA-BDS has served as a surgical bridge. It helped esophageal cancer patients awaiting esophagectomy to avoid nasogastric tubes, maintain enteral nutrition, and support tumor staging and neoadjuvant therapy without compromising surgery.

Compared with polymeric materials, metallic materials typically have superior stiffness and strength and are theoretically capable of providing better support to the lumen. Additionally, certain metals, such as magnesium (Mg), iron (Fe), zinc (Zn), and manganese (Mn), naturally exist in the human body. Therefore, the decomposition products of alloys made from these metals are nontoxic and can be metabolized and excreted from the body. Currently, Mg-, Fe-, and Zn-based composites are considered promising biodegradable metallic materials because of their excellent biodegradability and biocompatibility. They have been widely investigated in the field of vascular stents and orthopedic implants. However, their development for gastrointestinal stents is still in the early stages.

Iron, with its excellent biocompatibility, high modulus of elasticity, and high strength, has become one of the preferred materials for biodegradable metal stents. However, it is necessary to modify iron stents to accelerate corrosion due to their low corrosion rate and slow degradation. Adding small amounts of alloying elements such as cobalt, tungsten, carbon, and sulfur can accelerate the corrosion of pure iron and improve the mechanical properties of iron after rolling. Additionally, applying biodegradable polymer coatings to the iron surface can accelerate the corrosion of iron stents by acidifying the environment around the implant through hydrogen ions generated during the degradation of these polymers.

Zinc has a corrosion rate sufficient for the expected life of the stent, but its mechanical properties are weak, requiring modification to improve the mechanical parameters without affecting the corrosion rate. Yang *et al*[2] prepared a biodegradable Zn-0.4Mn-0.8Li alloy using a hot rolling process and confirmed that increasing the rolling temperature could correspondingly increase the alloy grain size. Furthermore, a multiscale structure with coexisting coarse and fine grains was obtained, and the synergistic effect of this multiscale structure and twinned grains significantly improved the strength and ductility of the Zn-0.4Mn-0.8Li alloy.

Magnesium has good biocompatibility and mechanical properties. However, the high corrosion rate of Mg-based materials limits their use in medical applications. Current research focuses on controlling the corrosion rate of Mg-based materials. Alloying and surface modification are effective strategies for improving the corrosion rate and mechanical properties of Mg. Mg-based alloys made from different metals in various ratios, such as AE21, WE43, AZ91, Mg-Nd-Zn-Zr (JDBM), and Mg-Zn-Y-Nd (ZE21B), can enhance biocompatibility and corrosion resistance. Wang *et al*[3] reported the promising use of ZE21B alloy as a novel biodegradable esophageal stent material. It had good degradation stability and inhibited the growth of esophageal tumor cells, likely due to its alkaline degradation product (hydroxide radical [OH^-]), which improved the harsh acidic environment around esophageal cancer. Compared with unmodified stents, biodegradable hydroxide-magnesium fluoride ($Mg(OH)_2$-MgF_2) and graphene oxide-polytrimethylene carbonate composite coatings significantly reduced the corrosion current density of magnesium alloy stents, extending their support for at least eight weeks.

There is still a lack of convincing data proving that BDSs are superior to other types of stents in treating esophageal disease. Meta-analysis revealed no significant differences in clinical success or adverse event rates among SEPS, SEMS, and BDS for RBES. The goal of reducing endoscopic treatment has not yet been fully achieved, as the recurrence of dysphagia leads to patients needing to place BDS sequentially or undergo multiple dilatations. Therefore, there is a need to develop higher-performance biodegradable esophageal stents.

To overcome tissue hyperplasia and tumor overgrowth, drug-eluting stents are becoming popular in the development of new esophageal stents. These stents can continuously release antiproliferative or antitumor drugs locally, thereby maximizing the suppression of hyperplastic reactions and tumor cell growth, extending stent patency, reducing dysphagia recurrence, and even achieving cancer treatment and prolonging patient survival. Biodegradable drug-eluting stents prepared by coating Mg-based braided stents with PLGA containing PTX reduced inflammation and fibrosis in caustic-induced esophageal stenosis. These stents maintained esophageal patency during a three-week follow-up period. Combining stent implantation with brachytherapy is another viable method for improving the long-term patency of patients with malignant esophageal stenosis. Multiple studies have consistently shown that radioactive SEMS loaded with iodine-125 achieve better stent patency and longer survival rates than traditional SEMS without causing higher complication rates. In the future, the development of biodegradable radioactive stents will be a promising direction for new esophageal stents.

In recent years, scientists have been exploring new BDSs using advanced technologies. 3D printing combines computer-aided design, materials processing, and computer-aided manufacturing to create 3D objects by converting digital model files into machine-recognizable code. The materials used for 3D printing are diverse, including polymers, composites, metals, and alloys. Various 3D printing technologies, such as fused deposition modeling (FDM), inkjet printing, stereolithography (SLA), and 3D four-axis printing (3D4P), offer significant advantages over traditional methods like knitting, weaving, and laser cutting for creating complex structural supports. For example, 3D printing has been used to fabricate various tissue engineering stents with controllable pore sizes and porous structures, such as designing and creating porous structures for biodegradable iron stents to improve their corrosion rates. Fouladian *et al*[4] developed a polyurethane esophageal stent loaded with 5-Fluorouracil (5-FU) using 3D printing. *In vitro* studies demonstrated that the stent provided sustained release of 5-FU over 110 days and enabled continuous dispersion of 5-FU in contact with the esophageal mucosa. Additionally, the stent showed

good stability after sterilization with gamma or ultraviolet irradiation and during accelerated storage. Overall, 3D printing is a powerful tool for providing customized drug-eluting stents, enabling precise treatment of patients.

Tissue engineering is an interdisciplinary field that combines principles from life sciences, chemistry, and engineering to develop biological substitutes using biomaterials, cell factors, and cells to maintain, restore, or rejuvenate tissues. Stents, cells, and their combinations are the three main focuses of tissue engineering research. Stents are networks that provide temporary support for cell growth and differentiation. Ideal esophageal stents should consist of composites with tubular and nano-microporous structures that are biocompatible, biodegradable, and resistant to gastric reflux to ensure functional regeneration of esophageal tissue. Various materials, such as decellularized matrices, acellular patches, biodegradable synthetic polymers, and composites, have been investigated as stent matrices for accessing esophageal tissues. Of them, decellularized matrices and biodegradable polymers have received particular attention. In living organisms, the extracellular matrix (ECM) plays a role in maintaining the structural integrity of multicellular organisms, regulating the survival and differentiation of cells and tissues, and promoting the repair of damaged tissues. Decellularized matrices contain certain natural ECM components and are enriched in collagen, elastin, fibronectin, laminin, and growth factors. They mimic the biological and mechanical functions of the natural ECM and provide a 3D structure within an appropriate microenvironment that directs cell growth, orientation, and proliferation, ultimately forming a functional organ. Han *et al*[5] used decellularized dermal matrix sheets derived from bovine reticular skin, which were implanted into the resected area of seven Bama mini-pigs after esophageal ESD and secured with metal clips. There was no significant esophageal stenosis in the decellularized dermal matrix sheet group compared with 42.8% (3/7) in the control group. The degree of stenosis in the control group was greater than that in the decellularized dermal matrix sheet group (39.8% *vs*. 17.2%, P <0.01), demonstrating the excellent utility of decellularized materials in preventing esophageal stenosis. Although decellularized matrices have achieved some success in numerous applications, their weak mechanical strength, rapid degradation, heterogeneity of donor tissues, and restricted sources remain challenges. In recent years, the focus of research in esophageal tissue engineering has gradually shifted to biodegradable polymers. PLA, PLLA, PCL, PGA, PLGA, and poly-L-propylcaprolactone-co-caprolactone (PLLC) have been used in the manufacture of tissue engineering esophageal stents. PCL, PLLC, and PLLA stents modified with collagen or fibronectin were more favorable than unmodified stents for the adhesion, survival, and maintenance of mitochondrial function in porcine esophageal epithelial cells, smooth muscle cells, and fibroblasts. This may be related to the presence of R-arginine, G-glycine, and D-aspartic acid in collagen and fibronectin. Exploring suitable biodegradable materials, biological modification methods, and structural designs to meet the needs of cell adhesion and proliferation will be the focus of future research on tissue engineering esophageal stents.

In conclusion, ideal BDS should reduce the need for repeat endoscopic treatments, avoid complications from stent removal, and improve the quality of life for patients. They should also contribute to the reduction of health care costs and the improvement of resource utilization efficiency. Currently, PLLA, SX-ELLA, and various types of biodegradable metallic stents have shown promising results in treating esophageal stenosis. However, short-term stenosis recurrence after stent dissolution remains a significant drawback. Therefore, improving the radial force of BDS, such as by fabricating biodegradable metal stents with appropriate degradation rates, is a key area for future research. Additionally, biodegradable drug-eluting and radioactive stents are expected to address tissue proliferation after stent placement and provide palliative treatment for malignant esophageal stenosis. 3D printing offers the opportunity to develop novel, customizable BDS to better meet individual treatment needs. The important role of tissue engineering stents is their ability to promote the natural repair of esophageal injury, reduce tissue fibrosis, and prevent esophageal stenosis. Future research is expected to further explore these areas to develop biodegradable esophageal stents that are more suitable for clinical applications.

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Conflicts of interest

None.

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