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Review

A review of biodegradable biliary stents made of magnesium metals: Current progress and future trends

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Abstract

Biliary system, which is responsible for transporting bile from the liver into the intestine, is commonly damaged by inflammation or tumors eventually causing liver failure or death. The implantation of biliary stents can effectively alleviate both benign and malignant biliary strictures, but the plastic and metal stents that are currently used cannot degrade and nearly has no beneficial biological effects, therefore their long-term service can result into inflammation, the formation of sludges and re-obstruction of bile duct. In recent years, magnesium (Mg) metal has been received increasing attention in the field of biomedical application due to its excellent biocompatibility, adequate mechanical properties, biodegradability and other advantages, such as anti-inflammatory and anti-tumor properties. The research on biliary stents made of magnesium metals (BSMM) has also made significant progress and a series of experiments in vitro and vivo has proved their possibility. However, there are still some problems holding back BSMM's clinical use, including rapid corrosion rate and potential harmful reaction. In this review, we would summarize the current research of BSMM, evaluate their clinical benefits, find the choke points, and discuss the solving method.

Keywords: Biliary stents; Magnesium metals; Degradation; Biological application.

1. Introduction

Biliary stents have been widely used in the treatment of biliary related disease such as benign and malignant biliary strictures, biliary fistulas, and others. They are mainly implanted and replaced through percutaneous transhepatic biliary drainage (PTCD) and endoscopic retrograde cholangiopancreatic intubation (ERCP), exhibiting minimal trauma and satisfactory results [1–3]. At present, the main materials for biliary stents are nickel titanium alloy, stainless steel, and plastic, which are non-absorbable. For benign biliary stricture and leakage, long-term placement of above stents can lead to the formation of bile sludge, biliary tract infection, hyperplasia, restenosis of the biliary tract, and even cholangiocarcinoma [4–6]. They also require endoscopic or surgical removal, which increases the treatment cost and risk . For patients with malignant biliary obstruction that cannot be surgical resected, the use of biliary stents can effectively relieve the obstruction and significantly extend the survival time [7–8]. Combining with the targeted therapy and immunotherapy, some patients are able to gain opportunity of surgical treatment [9–11]. However, long-term implantation of stents

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may result in local inflammation and bile sludge, and the tumor would grow into the stent, causing bile ducts to be blocked again. Moreover, non-absorbable stents remained in biliary duct would increase the difficulty of surgical treatment. If there is a type of material with good biocompatibility, biodegradability, mechanical properties, inhibition of inflammatory reactions, antibacterial properties, and even anti-tumor effects, it would be the ideal to be used as biliary stents to solve the above clinical problems.

The Mg metal has been increasingly valued as a biomaterial in recent years. Many scholars have conducted a series of studies on its applications in cardiovascular, orthopedic, dental, plastic surgery and other fields. Nowadays cardiovascular stents and orthopedic implants made of Mg metal are on the market [12–15]. Some people believe that biliary stents made of Mg metal(BSMM) may also have favorable prospects. For example, researchers have implanted Mg-6 wt.%Zn alloy and AZ31 alloy biliary stents into the common bile duct (CBD) through the duodenum and the incision site of CBD of New Zealand rabbits, respectively. The Mg-Nd-Zn-Zr alloy (denoted as JDBM) biliary stents made with mesh weaving carving technology had been implanted into the beagles with benign biliary stricture to test their corrosion resistance, biocompatibility and impact on bile duct tissue healing [16–21]. In this review, we not only summarized the research progress of BSMM and compared their advantages with currently used biliary stents, but also their application limitations and corresponding solutions.

2. The excellent properties of Mg metal and its advantages as a new material for biliary stent

2.1. Biological degradability

The Mg metal can degrade during in vivo service process, therefore, the appropriate degradation rate is the key for Mg metal to be used in biliary stent. After implanting the tubular stents made of Mg-6Zn alloy into the CBD of New Zealand rabbits through the duodenum, the stent maintained ~82% and 50% of its original length, and ~90% and 43% of its original volume at 1 and 2 wk after surgery, respectively. However, the remaining weight of stent is only ~ 9% after 3 wk [18]. After implanting the tubular stents made of AZ31 alloy at the incision site of the CBD of New Zealand rabbits, the remaining volumes of alloys were 93.82 ± 1.36% and 30.89 ± 2.46% of the original after 1 month and 3 months, respectively. There were apparent corrosion emerging at both ends of the stent possibly by the influence of fluid or local inflammation [19]. In addition to the above two in vivo presentments, scholars from Shanghai Jiaotong University had conducted in vitro dynamic corrosion experiment on JDBM alloys in which the mesh-like biliary stents were immersed into human bile. After 4 wk, the JDBM stents lost their metallic luster and were covered with degradation products and bile components. At 8th wk, localized corrosion pits emerged mainly at the connection points of stents. At 12th wk, the morphology of the stents was damaged, indicating that the stents had lost its function. Energy dispersive spectrometer (EDS) results showed that the corrosion products of JDBM alloy were mainly composed of O, C, Na, Mg, Ca, P, Cl, and Si. Based on the results from the in vivo experiments, JDBM stents seemed to corroded faster in vivo compared to in vitro environment. There are several factors may be responsible for the difference. First, the process of degradation in vivo is more complex than that in vitro, which can be influenced by bile irregular fluid flow, peristaltic movement of the bile duct wall, visceral compression, and human activities. Second, the fracture of the connection points of hand-woven stents promote their collapse, which is considered as a weakness of hand woven stents [21].

Bile is a weakly alkaline fluid with a pH between 7.6 and 8.6, containing abundant electrolytes, bile salts, cholesterol, bilirubin, and bile acids. Healthy adult secretes about ~800–1200 ml of bile every day [22]. Thus, the biliary environment also exhibits a strong corrosive effect on Mg metal. Peng et al. found that the degradation products formed by Mg2wt.%Zn alloys in the bile consisted of three layers, including organic matters (fatty acids, etc.), calcium and magnesium phosphate, and $Mg(OH)_2$/MgO. The multi-layer degradation products could slow down the corrosion rate[23]. Moreover, Liu et al. reported that the formation of $Mg\ (H_2PO_4)\ _2$ in the degradation product of WE43 alloys can decrease the corrosion rate when they were immersed in human bile [24]. These studies showed that Mg metals exhibit biodegradability in the biliary environment, and the degradation rates vary based on material compositions and shapes. After early degradation, they can form a stable protective film on surface to slow down this reaction. Therefore, Mg metal also possesses gradually changing biodegradable rate in the biliary environment [25].

2.2. Adequate mechanical properties

Plastic biliary stents are inexpensive, but possess poor mechanical properties. Nitinol alloys and other metal materials have good mechanical properties, but cannot degrade. Mg metals are not only biodegradable, but also have much better mechanical properties than plastics . Among the mechanical properties of Self-expandable metallic stents(SEMS), radial force (RF) and axial force (AF) are the most important parameters of their performance [26]. These parameters are strongly influenced by the stent materials and structures. Guo et al. prepared some mesh stent of JDBM by hand-woven technology through the cylindrical copper tube mold. They used a plane strain compression equipment to measure and compare the radial compression force of JDBM, coated JDBM stents and clinically commonly used nitinol stents, and the results showed that the force of JDBM, coated JDBM stents is much greater than nitinol stents, which mean value is about 4.43, 4.59, 3.75 N respectively. The stress retention rates were also compared and both materials exhibited good results of over 90%, indicating that JDBM alloy has enough mechanical strength to be used as biliary stents [21]. Zhang et al. used mechanical finite element simulation to optimize BSMM's mechanical performance, and showed that increasing the ovality of the bile duct would increase the difficulty of stent expansion. The use of zero order algorithms can effectively reduce the maximum equivalent stress acting on the stents, making the stress distribution more uniform and effective. Therefore, the optimized design of BSMM can effectively increase its support strength [27]. Furthermore, new alloy design, heat treatment and plastic deformation techniques can significantly improve mechanical property of Mg metals [28]. In 2017, a new approach was introduced that combined the strengthening benefits of nanocrystallinity with those of amorphization to produce a dual-phase material, which can make Mg alloy get near-ideal strength of 3.3 GPa at room temperature without sample size effects [29].Therefore, Mg metals can achieve adequate mechanical force to afford the effective supporting of biliary duct.

2.3. Excellent biocompatibility

Currently, the biocompatibility of BSMM has been extensively verified, including Mg-6Zn, AZ31 and JDBM alloys. In the in vivo experiment of Mg-6Zn alloy biliary stents, there was no significant difference in the expression of basic fibroblast growth factor (bFGF) and transforming growth factor beta(TGF-β) between Mg-6Zn and stainless steel groups at 1 and 2 wk post-surgery, indicating that Mg-6Zn alloy did not affect the healing of CBD. Blood biochemical tests were conducted to determine the levels of serum magnesium, creatinine (CREA), blood urea nitrogen (BUN), lipase (LPS), total bilirubin (TB), and alanine aminotransferase (GPT). Histological evaluations of the CBD, liver, and kidneys were also performed. These results indicated that the implantation and degradation of Mg-6Zn biliary stents did not affect the function and morphology of these organs [17]. Blood tests of the New Zealand rabbits received AZ31 alloy stents implantation at the incision site of the CBD showed that although stents may cause local inflammatory reactions during degradation, inflammation decreased to normal levels after 3 months of implantation [19]. Another experiment proved that JDBM showed good biocompatibility, as it did not cause adverse effects on the healing of local tissues and important organs after being implanted into the CBD in beagles. The JDBM even showed better biocompatibility compared to Zn-3Cu alloy based on in vitro MTT results [20].

The nickel titanium alloy, due to its excellent mechanical and flexible properties, is the most commonly used biliary stents material at present. It has good biocompatibility in the early implantation process. However, after long-term implantation, its mechanical compression and foreign-body reactions lead to tissue proliferation, inflammation, stone formation and siltation, eventually resulting into re-obstruction of the biliary tract. A series of in vivo experiments have confirmed that 1ong-term retention of Mg metal in the biliary duct did not cause obvious inflammation, tissue proliferation, and bile sludge formation [30–33]. The good biocompatibility of Mg metals in biliary circumstance is possibly due to the following two reasons: (1). The dynamic fluid in the biliary tract reduces local inflammatory reactions caused by the accumulation of degradation products, especial alkalide; (2). Mg^{2+} with an appropriate concentration can adjust the polarization state of macrophages from M1 which mainly release inflammatory mediators to M2 which release factors that promote tissue healing [34–37]. The current in vitro and in vivo researches on the biocompatibility and biodegradation of Mg metals in biliary circumstance are listed in Table 1 [16–21,23].

2.4. Antibacterial effect

In clinical practice, after the implantation of biliary stents, intestinal bacteria can reflux into the bile duct and cause biliary infection. Subsequently, biofilm and hard shell forming on the biliary stents and sediment forming in the bile duct would result in biliary obstruction again [38–40]. In 2010, Robinson et al. reported that Mg metal can significantly inhibit the growth of *E coli, Pseudomonas aeruginosa*, and *Staphylococcus aureus*. The degradation of Mg metals caused a change of bacteria's living environment, mainly an increase of the pH value. For most bacteria, suitable pH range for their growth is from 7.2 to 7.6 [41]. When the pH exceeds this range, antibacterial action will be gradually achieved. Many researches reported that an increase in pH to ≥ 9 could result in an obvious inhibitory effect on the growth of bacteria in the in vitro models [42,43]. Therefore, Mg may act as a new antibacterial agent differing from traditional antibiotics and not easily developing resistance. A lot of researches confirmed the antibacterial effect of nano MgO and Mg $(OH)_2$. The adhere of nanoparticles to the surface of bacteria disrupts the integrity of cell walls and ultimately lead to bacterial death. Consquently, Mg has antibacterial properties whether it is used as the main body of biomaterial, coating component, or nanoparticle [41,44–48]. The particle size, generation of reactive oxygen species, alkalinity of the medium, and concentration of Mg^{2+} are important factors determining the antibacterial activity of Mg-based materials [49]. Some researchers had also tried to enhance the antibacterial ability of Mg-based biomaterials by adding alloying elements such as Zn and Ag, or antibacterial coatings such as plasma electrolytic oxidation (PEO) coating or bioglass (BG)–iron oxide (Fe_3O_4) nanocomposite coating [50–53]. Therefore, excellent antibacterial performance is another significant advantage of BSMMs, as they can be used to treat or prevent biliary tract infections.

2.5. Anti-tumor effects

In the recent years, there have been numerous studies on Mg metal's significant inhibitory effects on the growth of various types of cancer [54–59]. Malignant tumor cells prefer to carry on anaerobic glycolysis to maintain energy supply so as to lead to an acidic tumor microenvironment, which can promote tumor cell proliferation and metastasis, inhibit the tumor killing activity of cytotoxic lymphocytes and NK cells, and increase resistance to chemotherapy and radiation therapy [60–62]. Mg metal can degrade in biliary duct, causing alkalization, an increased Mg^{2+} concentration and generation

Table 1
Summary of in vitro and in vivo researches on BSMM.

Materials	Corrosion rate in vitro	Animal model	Length of days	Design of sample	Corrosion rate in vivo	Biocompability findings	References
Mg-6 wt%Zn	–	CBD of New Zealand rabbits	3 wk	Tubular shape	~89, ~42 and ~9% of the original weight were retained respectively at 1, 2 and 3 wk post-surgery	At 3 wk post-surgery, the CBD was completely healed with adverse influence	[17]
Mg-6 wt%Zn	1.82, 1.05 mm/year (immersion test in bile, test duration: 7, 10 days)	Implantation in CBD of New Zealand rabbits through duodenal incision	3 wk	Tubular shape	0.107 mm/year	The results of serum total bilirubin (TB) indicated that TB value at 1 wk postoperation was slightly higher than the pre-operative values. At 2 and 3 wk post-operation, there was no significant difference observed ($P < 0.05$).	[18]
Mg-6 wt%Zn	–	Implantation in CBD of New Zealand rabbits through duodenal incision	3 wk	Tubular shape	–	After 3 wk, no stone, bile sludge and degradation product were found both in CBD and gallbladder. Mg–6Zn stents neither affected important bio-chemical parameters, nor harmed the function or morphology of the CBD, kidney, pancreas or liver.	[16]
Mg-2 wt%Zn	1.22, 0.52 mm/year (immersion test in bile, test duration: 7,15 days)	The animal used in this experiment was a white pig weighing 50 kg. Its CBD was incised and placed into MZ2 biliary stent, and then surgically sutured.	3 wk	Tubular shape. (two ends were covered with latex tubes to avoid its displacement)	0.83 mm/year (The degradation product film consisted of three layers, including organic matter (fatty acid, etc.), phosphate of calcium and magnesium, and $Mg(OH)_2$/MgO from outside to inside.	Its good biosafety was proved by histological tests of CBD tissues and major organs, and the surgical wound of the bile duct epithelial tissue healed well within postoperative 3 wk.	[23]
AZ31	–	Implantation in CBD of New Zealand Rabbits via the incision of anterior wall of the distal CBD	6 months	Tubular shape.	Micro-CT 3D reconstruction demonstrated a remaining volume of 93.82 ± 1.36% and 30.89 ± 2.46% after 1 and 3 month, respectively.	H&E staining (bile duct, liver, gall bladder and duodenum, heart and kidney) and whole blood analysis (serum magnesium, white blood cells, liver and kidney function) confirmed the biosafety of AZ31 biliary stents.	[19]
Mg-Nd-Zn-Zr alloy (JDBM)	2.199, 0.733 mm/year (pure and the coating (MgF_2-PDLLA) respectively, immersion test in bile, test duration: 10 days)	Implantation in CBD of beagles via the incision of CBD	3 months	Cylindrical sample	3 months after stent placement, the stents in the CBD retained most of its volume	Neither the JDBM alloy nor the coating (MgF2-PDLLA) JDBM alloy affected the function or morphology of the bile duct, liver, kidney or spleen.	[20]
Mg-Nd-Zn-Zr alloy (JDBM)	–	Beagle's CBD was semi-ligated to establish the model of incomplete biliary stricture. Biliary stent was placed into the CBD through the stricture site	60 days	The mesh stent by hand-woven technology	Sixty days after stent placement, the stent in the CBD was completely degraded	Biosafety was demonstrated by biochemical results, the general state of animals, the results of HE staining of bile duct and important organs	[21]

of hydrogen gas. $Mg(OH)_2$ can significantly transform acidic environment into alkaline one to inhibit or even kill tumor cells [63–65]. Multiple studies have also shown that hydrogen gas can inhibit oxidative and inflammatory responses and upregulate the expression of p53, a tumor suppressor protein, thereby achieving anti-tumor effects [57,66–68]. Some scholars have revealed that Mg^{2+} can regulate cellular biochemical reactions of various tumors, including inhibiting tumor proliferation and metastasis, regulating tumor cell cycle and apoptosis, promoting DNA replication and repair, and reducing inflammation and oxidative stress responses [69–72]. Moreover, recent study showed that the binding of co-stimulatory cell surface molecule (LFA-1) on CD8+ *T* cells with Mg^{2+} can activate CD8+ *T* cells to exhibit specific cytotoxicity to kill tumor cells. In clinical practice, low serum Mg^{2+} levels are associated with faster disease progression and shorter overall survival in cancer patients treated with CAR T cells and immune checkpoint antibodies [73,74]. In addition, Mg^{2+} can enhance the effect of some chemotherapy drugs. For example, Mg^{2+} can enhance the tumor killing effect on colon tumor and prevent nephrotoxicity of cisplatin. Combinational use of $MgCl_2$ and sodium valproate (VPA) can significantly reduce the proliferation, migration and tumorigenicity of human bladder tumor cells in vivo [75,76]. More recently, Li et al. found that Mg extraction inhibited the proliferation of human cholangiocarcinoma cells and induced their apoptosis, and Mg plates inhibited cell adhesion and disrupted the cytoskeleton during degradation. In animal experiments, Mg or Ti wires were implanted into the nude mice beared with H22 liver tumors. After 15 days, the average volume and weight of tumors in the Mg group were significantly smaller than those in the Ti group. Histopathological analysis showed a significant increase in apoptosis of tumor cells around Mg wires [77]. Peng et al. reported that degradation products of high-purity Mg wires can also inhibit proliferation and induce apoptosis of gallbladder cancer cells. Local high alkaline environment ($pH = 8.1$) inhibits tumor cell proliferation by blocking the G0/G1 phase of cell cycle [78]. Therefore, BSMMs could not only provide temporary support, but also kill local tumors . Their degradation can generate local high concentration of Mg^{2+}, which maybe enhance anti-tumor effects of systemic chemotherapy and immunotherapy. The clinical effect and molecular mechanism are still unclear and should be further explored .

3. Clinical applications of BSMMs

Due to so many advantages, BSMMs have been received much attention and become a popular research field. Recently, UNITY-B, a balloon expandable biodegradable biliary stent made of Mg-Nd-Mn alloy with a polymer coating on the surface developed by Q3 Medical Equipment Co., Ltd., has obtained Conformité Europée ne(CE) certification for the treatment of biliary strictures and fistulas. The clinical study to evaluate its safety and efficacy showed that the success rate of its final clinical evaluation was 94.4% with no significant adverse events, a prominent result compared to the ESGE 2012 traditional product guidelines [79,80]. Sundeep Lakhtakia et al. reported a case that a 26-year-old female developed a complication of postcholecystectomy perihilar benign biliary stricture. Treatment with balloon dilation and plastic stent placement under ERCP was ineffective, and treatment with a covered Ni-Ti biliary stent may give rise to contralateral bile duct obstruction. After the evaluation, she was treated with a stent-in-stent "Y shaped" configuration with two UNITY-B stents which reopened the bile duct of hepatic hilum (Fig. 1). Her liver function was recovered 2 wk later, and she felt comfortable after 8 wk of implantation with normal biochemistry results. The biodegradable biliary stents do not need surgical removal, thus significantly reduce patient's pain and cost [81]. Although preliminary clinical validation of UNITY-B has been obtained, its long-term and real-world clinical application situation still requires further observation.

4. Scientific problems and future research directions faced by the application of BSMM

BSMM has shown promising perspective, however, there are the key factors determining whether it can be widely used are unclear, including its corrosion resistance in the biliary environment, its biologic effects and mechanisms on biliary inflammation, healing and tumors .Therefore, we believe that the following important scientific issues deserve further exploration and settlement.

4.1. Resolve the problem of rapid corrosion rate to ensure sufficient service time

So far, no case with complication of biliary stricture of BSMMs was reported in animal experiments. However, from clinical experiences, the stent service time should be minimum 6 months or even 1 year to ensure clinical safety, because of possible delayed scarring and stricture of the bile duct caused by short-term service [22,82,83]. As clinical surgeons, we have seen a few patients with biliary stent displaced 2 months after implantation, still facing biliary stenosis. According our clinical experience, the optimum duration of Mg stent implanted in patients with benign biliary diseases is more than 3–6 months but no longer than 1 year. In the light of traditional ideas, non-degradable metals are used in the patients with malignant diseases, which can afford long-time supports . However, due to the progress of systematic therapy, patients may get the effective treatments and the chances of surgery, so biodegradable metals can also be used in patients with malignant diseases. The duration should be more than 2–3 months, because the valid therapeutic effects may be attained after at least 2–3 months. Based on current reports studying the corrosion time of various BSMMs in biliary circumstance, the service time was normally between 1 and 6 months and the longest one was JDBM which could not last for more than 6 months. The corrosion rates varied greatly, mainly related to alloy preparation methods and experimental conditions (e.g., corrosive medium, static or dynamic environment, experimental duration, and animal selection). Though

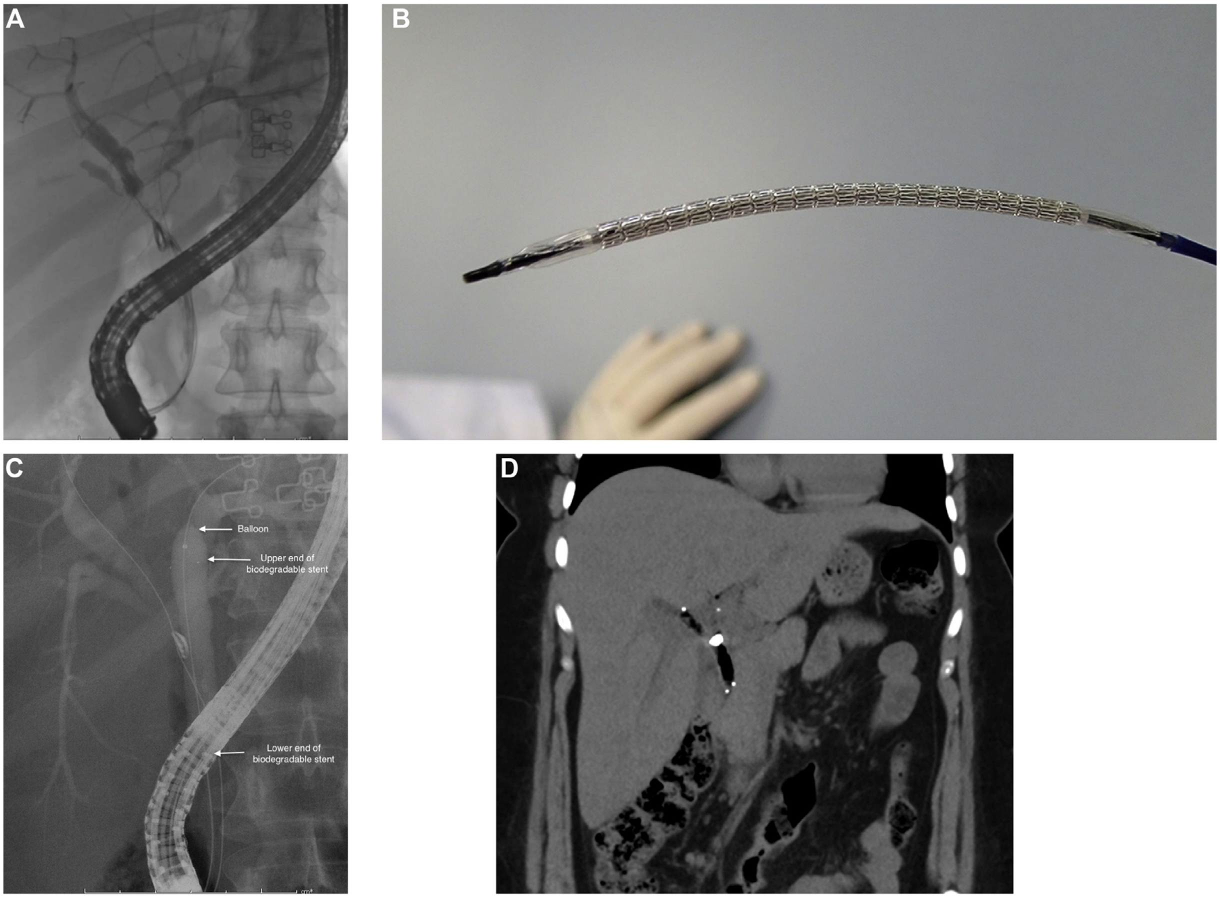

Fig. 1. Illustration of the successful treatment of a postcholecystectomy perihilar benign biliary stricture in a 26-year-old female using two UNITY-B stents in a 'Y shaped' configuration, resulting in bile duct reopening, liver function recovery, and patient comfort without surgical removal.

these experiments cannot fully simulate the realistic condition of the human biliary tract, they are relatively close to clinical conditions. Moreover, quick degradation rate at the early stage would cause locally high concentration of Mg^{2+} and pH value that would negatively affect the proliferation, junction, and angiogenesis of epithelial cells, as well as the formation and maturation of collagen, resulting in prolonged wound healing. Nowadays, there are several methods to adjust the corrosion resistance of Mg metals: (1). Microalloying with adding trace amounts of non-rare elements such as Ca, Ag, Zn, Mn, Sr, and Zr into Mg alloys, can suppress the second phase at grain boundaries and increase the electrode potential of the alloy, thus suppressing local corrosion reactions. Adding elements that are easy to passivate can improve the alloy's passivation ability, forming a complete and compact passivation film on the surface, thereby reducing its corrosion rate [84–88].The concentration of alloying elements increases the density of the surface oxide film, thus enhancing the protective effect of Mg oxide and the corrosion resistance of Mg alloys. In addition, adding rare earth elements (REEs), such as La, Ce, Er, Ho, into biomedical Mg alloys often exhibit an act as "scavengers", promoting the formation of more stable oxide films and reducing the occurrence of micro current corrosion between Mg and impurity elements. Although light rare earth elements are toxic, heavy ones are commonly used due to their high solubility and difficulty in forming intermetallic compound phases [25,89–92]; (2). The preparation of coatings is another effective method to develop the corrosion resistance . The coating on Mg metal can be divided into three categories based on whether the magnesium matrix participates in the formation of the coating: substrate related coatings, non-substrate related coatings, and composite material coatings [93]. Chen et al. reported that of JDBM coated with MgF2-PDLLA significantly enhanced the corrosion resistance compared to bare JDBM. After 90 days of in vitro bile immersion, the corrosion rate of coated alloy was about half of the bare one, with values of ∼0.652 and 1.140 mm. year-1, respectively. At 3 months after implantation in beagles' biliary ducts, the cracks on the surface of the bare stents were deeper than the coated ones [21]. Zan R et al. have developed a lotus-like nanocomposite coating on the Mg substrate by integrating poly-trimethylene carbonate with covalent organic frameworks (COF). The coating possessed self-polishing property and optimal surface energy, which can decelerate degradation rate and inhibit the formation of biofilm [94]. Coating can also be loaded with drugs to enhance the therapeutic effect. The functional coatings on biliary stents mainly include seven categories: anticorrosion, -bacterial, -tumor, stone-dissolving, X-ray visibility, anti-stent migration and functional composite coatings [95]. For example, the coatings loaded with pa-

Table 2
the researches on improving the corrosion rate of JDBM by various methods.

Method	Media	Corrosion test	Test time	Corrosion rate	Effect on corrosion resist	Reference
JDBM alloy	Hank's solution	Immersion test	10 days	0.28 mm/year	Improved (AZ31 alloy 1.02 mm/year)	[102]
MgF_2-PDLLA coating	Human bile	Immersion test	3 months	0.652 mm/year	Improved (uncoated alloy 1.140 mm/year)	[20]
$SrHPO_4$ coating	Hank's solution	Immersion test	10 days	0.18 mm/year	Improved (uncoated alloy 0.52 mm/year)	[103]
Preparation (extrusion and heat treatment)	Simulated body fluid	Immersion test	10 days	~0.21–0.28 mm/year	Improved (as-cast alloy ~0.37 mm/year)	[104]
Calcium phosphate coating	Hank's solution	Immersion test	10 days	0.39 mm/year	Improved (uncoated alloy 0.54 mm/year)	[105]
Mg-Al-layered double hydroxide coating	phosphate buffer saline	Hydrogen evolution test	28 days	~0.5 $mg \cdot cm^{-2} \cdot d^{-1}$	Improved (uncoated alloy ~1.2 $mg \cdot cm^{-2} \cdot d^{-1}$)	[106]
Preparation (extrusion)	Simulated body fluid	Hydrogen evolution and mass loss tests	10 days	~0.1– 0.225 mm/year	Improved (as-cast alloy ~0.37 mm/year)	[107]

clitaxel significantly inhibited esophageal hyperplasia and reduced the incidence of esophageal stenosis [96]. Many reports proved that chemotherapy drug-eluting stents not only prolong stent patency, but also improve the prognosis of related cancers [97]. Types of coatings should be according to their requirements of application, such as the implantation site, normal or pathological condition, and the required service time; (3). Advanced preparation methods, such as severe plastic deformation (SPD) including equal channel angular pressing (ECAP) and high-pressure torsion (HPT), have been confirmed that can improve Mg metal's corrosion resistance. SPD can significantly refine and homogenize the grain, with a good impact on corrosion resistance and pitting sensitivity. On a more uniform surface, corrosion often transits from localized corrosion to uniform and general corrosion. Thus, increase in grain boundary density can lead to the formation of passivation film and improvement of adhesion [98–101]. The products with decreased corrosion resistance after SPD are mainly related to ECAP, most likely due to the lack of significant refinement of grain and/or uneven grain structure [102,103]. There are aslo reports that friction stir processing and multi axis isothermal forging processing can improve the corrosion resistance of Mg metal [104,105]; (4). The structural design is an useful way to extend the biodegradable stents' lifespan. Stress corrosion cracking (SCC) is the fracture of Mg metal under tensile stress and highly sensitive environments. Research has showed that the SCC of Mg metal in corrosion media is mainly caused by pitting corrosion and the rupture of surface film under stress deformation. Micro current corrosion could accelerate the fracture of stress concentration site. Therefore, an ideal design that reduces the formation of stress sites can prolong the service life of BSMMs [106]. Taking JDBM as an example, the researches on improving its corrosion rate by various methods are listed in Table 2 [107–112]. Degradation rate and the potential biological effects of Mg implant should also be considered together. If the implant has a very rapid degradation rate, It may not only lead to the remarkable inhibition of tumor growth and bacterial proliferation, but also the collapse of the structure before the recovery of the physiological organ. If very slow, it may not cause the effective therapeutic effects. For this reason, alloys which have the right degradation rates ought to be researched and prepared. We assume that using appropriate methods of corrosion modification can make BSMMs achieve the clinical requirements and generate the satisfactory functions.

4.2. Biological behavior of BSMMs in biliary environment are difficult to be assessed

At present, BSMMs are still in the research and demonstration period, and the research on their biological behavior mainly focuses on in vitro 2D cell culture and in vivo animal's bile duct implantation experiments. In vitro 2D experiment is instant and technically convenient, but it is difficult to simulate the interaction between materials and different cells in real biliary environment. Biliary tumor cell lines are able to provide some information but are difficult to fully reflect the heterogeneity of tumors [113,114]. In vivo experiments have been criticized for their high requirements of experimental conditions, ethics, distinct individual differences in animals and difficulty in dynamic observation. Thus, it is crucial to establish an in vitro biosimulation system to study the biological reaction of Mg metals in biliary environment. In recent years, organoids and organ chips have received great attention by researchers, and were used to study biomimetic and drug therapeutic effects of cardiovascular, respiratory, digestive systems and so on. [115–119]. Ren et al. reported that they had established organoids derived from bile duct cancer samples of 61 patients (PDOs) and verified that organoids' histological and genetic characteristics were similar to the corresponding primary tissue samples. This model was used for chemotherapy drug screening and the results were clinically validated in 92.3% (12/13) of patients, indicating it should be a highly realistic and suitable model for in vitro research on bile duct cancer [120]. Previously, the 3-D cultured cancer organs in vitro contain only tumor epithelium and sometimes require artificial reconstruction with the tumor microenvironment (TME). PDOs propagated by an air-liquid interface (ALI) method not only preserved the parenchyma

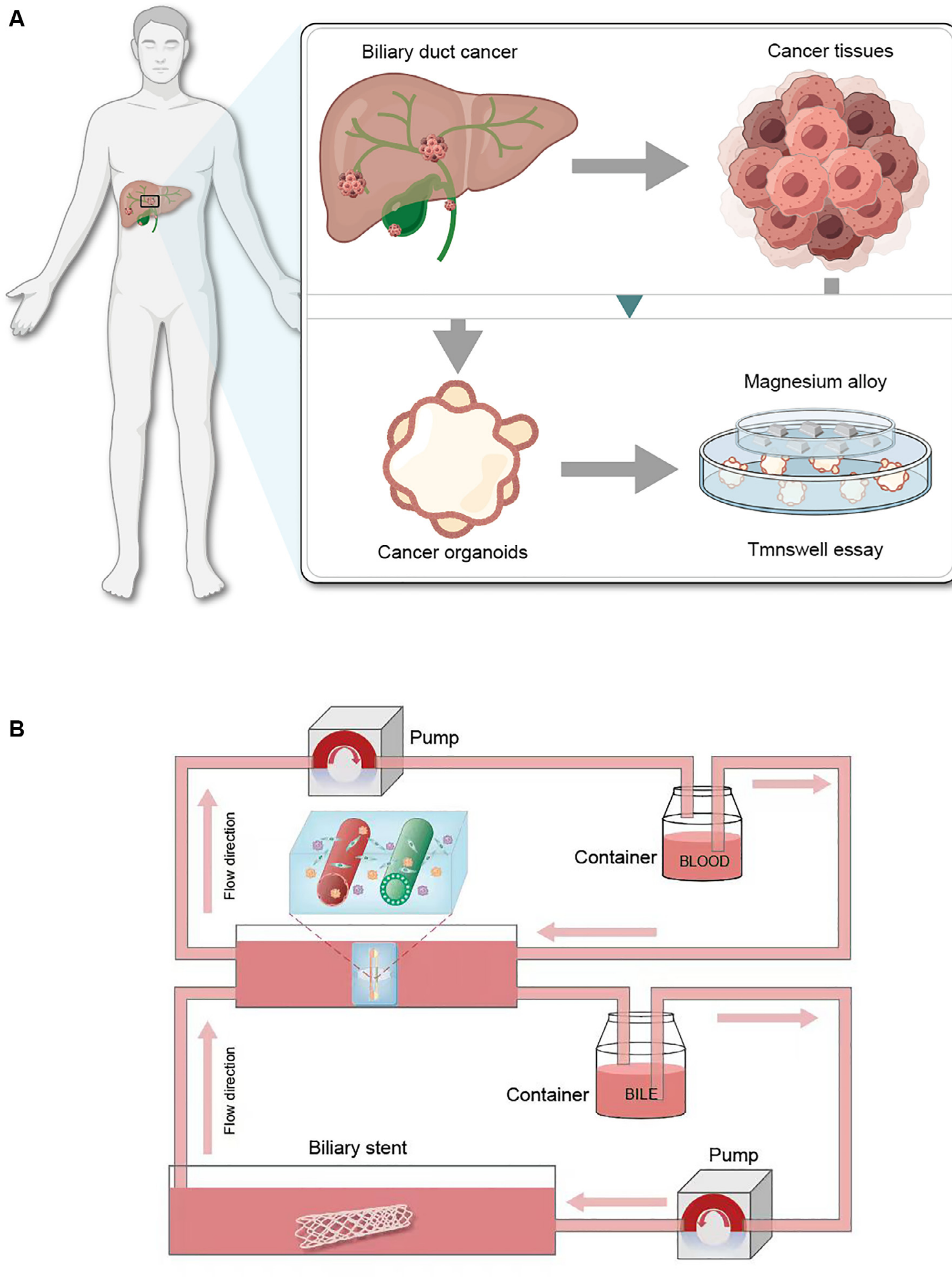

Fig. 2. Illustration of the current research projects involving BSMMs and organoids or organ chips, demonstrating the potential for these methods to advance understanding and treatment strategies for biliary diseases and tumors, as well as the potential effects of Mg metals on tissue healing.

and stroma of the tumor, but also had complex tumor microenvironment structures, including tumor-infiltrating lymphocytes(TILs). Real time single-cell assays of gene expression and immune system confirmed that PDO TILs accurately preserved the original tumor T cell receptor (TCR) spectrum. This organoids with immune cells successfully simulated the immune checkpoint blockade (ICB) process using anti PD-1 and/or anti PDL1 antibodies to block the points, activated tumor specific antigen TIL, and induced tumor cytotoxicity [121]. Moreover, some researchers have confirmed that

Mg metal was able to depress liver and gallbladder tumors. However, its specific effects and mechanisms of action on tumor cells, impact on tumor microenvironment, and synergistic effects with chemotherapy and immunotherapy still need to be further verified and studied by establishing a highly biomimetic system. The above type of organoids could provide a good in vitro research platform for the use of BSMMs in the treatment of biliary tumors. In 2020, Du et al. reported a biliary chip that not only replicated the 3-D tubular structure of the biliary system, but also possessed epithelial barrier function. The mouse bile duct cells in the channel of the device became polarized and formed mature tight connections. A series of follow-up experiments have confirmed that this bile duct chip has the basic structure and organ function of the extrahepatic bile duct, and can serve as an ideally new platform for studying the pathophysiology of bile ducts using bile duct cells derived from different sources. It was also reported that a human vascularized bile duct chip (VBDOC), including polarized bile ducts, blood vessels, fibroblasts, various inflammatory cells, and fibrous stroma, can simulate the flow of blood and bile as well as different reactions of endothelial cells. This chip can be used to study the mechanical and inflammatory responses of the bile duct to different simulations, including cytokine secretion and immune cell recruitment. They also successfully constructed organoid chips with cells isolated from the bile duct tissue of patients with primary sclerosing cholangitis (PSC). Liver tissue explants, postoperative biopsy, common bile duct bristles, and induced pluripotent stem cells can all be included as cell sources as needs. Thus, VBDOC may represent as a new multicellular research platform for a variety of biliary diseases [122–124]. The high concentrations of Mg^{2+} and OH^- produced by Mg metals during early and rapid degradation can cause inflammatory reactions and affect the healing of biliary tissue. Therefore, the above research platform can be used to simulate this process in vitro for researchers to dynamically observe the activity of biliary epithelial and inflammatory cells and find an Mg metals with appropriate degradation rate that does not obviously affect tissue healing. In addition, many types of functional coatings were prepared for Mg metals,which need a more convenient and reliable detection method to prove their function and efficacy. The organ chips for the bile duct will be significant to test the application of Mg biomaterials in biliary tumor and tissue healing. The current research projects of BSMMs and organoids or organ chips are illustrated in Fig. 2.

5. Conclusion

In summary, BSMM has great potential and advantages over those stents currently being used. However, the feasibility and value of its clinical application still need further verification, with the main focuses on suitable corrosion rate, enough service time, favourable biological performance and rational design. With the continuous improvement of preparation and experimental methods, the research and development of BSMM can be accelerated. In the near future, the clinical use of BSMM would be achieved.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Ling Liu: Writing – original draft, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tuo En Liu:** Writing – review & editing, Supervision, Conceptualization. **Tan To Cheung:** Writing – review & editing, Supervision, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jma.2024.11.014.

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