

RESEARCH ARTICLE

3D-Printing-Assisted Extraluminal Anti-Reflux Diodes for Preventing Vesicoureteral Reflux through Double-J Stents

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Abstract: This paper presents novel umbrella-shaped flexible devices to prevent vesicoureteral reflux along double-J stents, which is a backward flow of urine from the bladder to the kidney and is a critical issue in patients with urinary stones. The anti-reflux devices were designed to mechanically attach to the stent and were manufactured using three-dimensional (3D) printing and polymer casting methods. Based on the umbrella shapes, four different devices were manufactured, and the anti-reflux efficiency was demonstrated through in vitro experiments using a urination model. Consequently, penta-shaped devices exhibited the best anti-reflux performance (44% decrease in reflux compared to the stent without the device), and maximum efficiency occurred when the device was attached near the bladder-ureter junction. In addition, a disadvantage of 3D printing (i.e., unwanted rough surface) helped the device strongly adhere to the surface of the stent during the insertion operation. Finally, long-term soaking experiments revealed that the fabricated devices were mechanically robust and chemically stable (safe) even being soaked in urine for 4 weeks. The findings of this study support the use of additive manufacturing to make various flexible and biocompatible urological devices to mitigate critical issues in patients with urinary stones.

Keywords: Vesicoureteral reflux; Double-J stent; 3D printing; Anti-reflux diode; Urology

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Received: December 21, 2021; **Accepted:** February 7, 2022; **Published Online:** February 7, 2022

Citation: Lee J, Sung J, Jo JK, *et al.*, 2022, 3D-Printing-Assisted Extraluminal Anti-Reflux Diodes for Preventing Vesicoureteral Reflux Through Double-J Stents. *Int J Bioprint*, 8(2):549. <http://doi.org/10.18063/ijb.v8i2.549>

1. Introduction

Most urological procedures and treatments, such as lithotripsy, ureteroscopic procedures, prevention of ureteral stenosis, relief of hydronephrosis, and reduction in urological complications, require double-J (DJ) stents^[1-7]. In general, these DJ stents are thin and hollow tubes with side holes composed of polyurethane material, and both ends are rolled up to hold the stent in the ureter^[8]. The DJ stents are located in the ureter to enable urine drainage from the kidney into the bladder and to prevent contraction of the ureter after the removal of urinary stones^[5,9]. In addition, ureteral stents are used during renal transplantation to reduce urological complications, such as anastomotic stricture or urine leakage after operation^[6,7]. Thus, DJ stents are necessary

medical tools for urologists during various urological procedures and treatments^[10]. Despite the advantages of using DJ stents, the inserted DJ stents can cause side effects in patients. For example, hematuria, dysuria, irritative urination, and urinary tract infection can result from inserted DJ stents^[4-7,9-13]. In addition, vesicoureteral reflux (VUR) is a side effect that frequently occurs because the stents preclude the complete closure of the bladder-ureter junction (vesicoureteric junction [VUJ]) during urination^[14-16]. VUR is a significant problem that leads to flank pain, pyelonephritis, renal scar formation, and renal failure^[15,17-20]. In particular, VUR induced by inserted stent can cause severe flank pain during urination or upper urinary tract infection, which has a potential hazard of pyelonephritis^[15,19-21]. In addition, occurrence of

reflux along the stents was reported in 51.4% of patients even after immediate insertion of ureteral stents^[22]. Although VUR associated with DJ stents would not require an immediate treatment or surgery to relieve the symptoms, repetitive VUR may adversely affect patients who require long-term placement of ureteral stents^[21,23]. Thus, for the quality of patients' life, the prevention of VUR is significantly important, and therefore, anti-reflux medical devices compatible with the DJ stents must be developed; this remains as a challenge in urology.

Once a DJ stent is inserted in the ureter, urine can flow either through the inner wall or outer surface of the stent (more specifically, the space between the outer stent wall and the inner wall of the ureter)^[24]. Due to the dilated VUJ, reflux can flow not only in the intraluminal space but also in the extraluminal space^[15,16]. To decrease the VUR, various types of anti-reflux devices integrated with DJ stents have been investigated for intraluminal reflux^[15,21,23,25-27]. For example, polymeric flap valves and collapsed valves have been demonstrated as intraluminal anti-reflux devices^[15,21,25,26]. For polymeric flap valve devices, in vitro experiments using hydrostatic pressure indicated that volumetric backflow rates were decreased by up to 8 times under 50 cm-H₂O pressure compared to a bare DJ stent with no valve. The membrane-type anti-reflux valves at distal end of the stent have also been studied and shown to reduce VUR degrees and frequencies^[23,27]. However, the valves were large, inducing discomfort and irritation symptoms in patients during the insertion and therapeutic period. Although the devices described in previous studies were effective in preventing intraluminal reflux, they could not prevent extraluminal reflux alongside the stent, which accounts for the majority of the overall reflux. In addition, from a clinical point of view, there is also a concern that extraluminal reflux may occur^[15,21]. To the best of our knowledge, there is currently no published study about the prevention of extraluminal reflux alongside the stent. Therefore, the development of small, flexible, biocompatible, and reliable anti-reflux devices with less irritation is still required to prevent extraluminal reflux alongside the stent.

In the last decade, additive manufacturing has been widely used to develop various medical devices such as bio-microfluidic chips^[28], dental implants^[29,30], custom prosthetics^[31,32], and even ureteral stents^[33]. In particular, casting processes using three-dimensional (3D)-printed molds have been utilized in a variety of fields because they allow the use of diverse materials, which differ from 3D-printed materials. For example, in medical devices, flexible or biocompatible materials, such as silicone, epoxy, and polydimethylsiloxane, were utilized as the casting material poured in 3D-printed molds^[34-36]. Among the various types of 3D-printing methods, the

fused deposition modeling (FDM)-type printing method has been commonly used owing to its simplicity, low cost, and fast printing speed^[37,38]. Moreover, products can be designed using computer-aided design (CAD) software to create the desired shape. The FDM method deposits a filament (e.g., polylactic acid or acrylonitrile butadiene styrene) layer-by-layer; however, the resulting product has a poor surface roughness^[38,39]. Recent studies have revealed that this drawback (i.e., rough surface) can be intentionally utilized for various applications such as (super) hydrophobic surfaces^[40], micro-drilling devices^[41], microchannels^[42], and non-sticky surfaces^[43].

In this study, we fabricated and demonstrated attachable extraluminal anti-reflux diodes (EADs) based on an umbrella shape, which can effectively prevent extraluminal reflux from the bladder into the kidney while allowing urine drainage from the kidney into the bladder. The EADs were based on four different types of polygonal shapes and were fabricated by a casting process using an FDM-type 3D printer. The Ecoflex elastomer was utilized as the main body material due to its good flexibility and biocompatibility^[44,45]. To demonstrate the diode performance, the devices were characterized using an in vitro voiding (urination) model to measure the maximum reflux height. In addition, the attached position of the diode on the DJ stent and the number of diodes were considered to investigate the maximum performance. The disadvantage of 3D printing (i.e., rough surface patterns) was intentionally used to effectively attach the diode onto the stent, and the mechanical properties were compared to those without rough surface patterns. To further investigate the health safety and durability of the devices in urine, Fourier transform infrared (FTIR) spectroscopy was conducted to observe changes in the chemical structures of devices immersed in artificial urine for 4 weeks.

2. Design and fabrication

Figure 1A shows an overall schematic of the EAD, which is an anti-reflux device integrated with the DJ stent in the ureter. Since the material of the EAD is Ecoflex, which is flexible, its shape can be easily deformed by pressure. **Figure 1B** presents the operational mechanisms for the forward flow (urine drainage) and backward flow (urine reflux). The mechanism is based on the change in the cross-sectional area (internal area) of the EAD with respect to the flow direction. During forward flow, the urine flows and pushes the outer wall of the EAD. As the EAD is pushed toward the stent, the internal area decreases and the external area (i.e., the area between the outer wall of the EAD and inner wall of the ureter) increases. Consequently, urine can readily flow along the external area in a forward direction. In contrast, during backward flow, the urine flows and pushes the inner wall of the EAD. Thus, the EAD expands and increases the internal area.

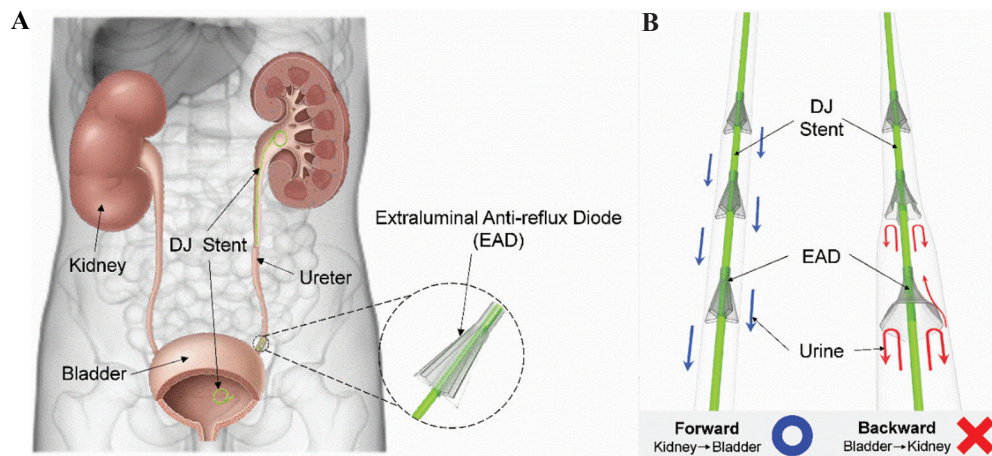


Figure 1. Conceptual illustration of the extraluminal anti-reflux diodes (EADs). (A) Schematic of the inserted EAD with the DJ stent in the urinary organs. (B) Working mechanism of the EADs for forward and backward flows.

Consequently, the external area is significantly reduced, and the flow resistance increases, such that reflux rarely occurs. Because the urine must pass through the inner space of the EAD in response to the applied reflux, the anti-reflux performance of the EAD highly depends on the cross-sectional (area) shapes. Hence, in this study, four different types of EADs (quadra-, penta-, hexa-, and octa-shaped) were fabricated and used to investigate the effect of the device shape on the anti-reflux performance.

To estimate the fluidic properties of the anti-reflux device with velocity and pressure fields across the EAD, a computer-aided engineering simulation was conducted using COMSOL Multiphysics, as shown in **Figure 2**. The penta-shaped EAD was used for the simulation. For forward flow (i.e., flow from the kidney to the bladder), the inlet pressure was set to 18 cm-H₂O owing to the renal pelvis pressure being approximately 15 – 18 cm-H₂O hydrostatic pressure when the stent was inserted in the ureter. For backward flow (i.e., flow from the bladder to the kidney), the inlet pressure was set to be 50 cm-H₂O of intravesical pressure on voiding^[16,21]. **Figures 2A and C** show the velocity streamline fields across the penta-shaped device under forward and backward flows, respectively. **Figures 2B and D** show the pressure distribution of the cross-sectional area observed in the forward and backward flow directions, respectively. Based on the simulation, for forward flow, the pressure of the external area was higher than that of the internal area, as shown in **Figure 2B**. This implies that the EAD can be contracted toward the stent because of its flexibility. Conversely, for backward flow, the fluid (i.e., urine) can be trapped inside the EAD, thus inducing high pressure in the internal area. This high pressure inside the internal area can push the penta-shaped membrane toward the ureter, as shown in **Figure 2D**. This result implies that the EAD can expand toward the ureter because of the pressure gradient in the ureter wall direction. Thus, the

designed anti-reflux device can rectify the desired urine flow in response to the flow direction.

The overall manufacturing procedure was based on casting methods using a 3D printer. The overall schematic of the fabrication process for the penta-shaped EAD is shown in **Figure 3**. FDM-type 3D printer (GUIDER II, FlashForge Co.) with polylactic acid (PLA) filament, which is a widely utilized filament for FDM printing, was employed to print casting mold and die (**Figure 3A**). The printing parameters, namely the extruder temperature, platform temperature, printing speed, layer height, and printing density, were set to 220°C, 40°C, 60 mm/s, 0.18 mm, and 15%, respectively. It should be noted that the shape of the PLA mold and die can be adjusted with respect to the final shape of the EAD (i.e., quadra, penta, hexa, and octa). After the PLA mold and die were printed, the prepared elastomer Ecoflex (00-50 type, Smooth-On Inc.), which was mixed in a 1:1 (part A: part B) ratio, was poured onto the printed PLA mold (**Figure 3B**). The poured Ecoflex was then degassed in a vacuum chamber for 10 min to eliminate air bubbles trapped in the liquid elastomer. After the degassing process, the printed PLA die was pushed into the mold; thus, a thin membrane of the Ecoflex could be formed in the clearance between the mold and die (**Figure 3C**). The Ecoflex was then baked on a heater at 50°C for 20 min for the curing process (**Figure 3D**). They can also be baked at high temperatures for fast curing. However, here, the shapes of the PLA mold and die can be deformed by a baking temperature higher than the glass transition temperature of the PLA. Consequently, the PLA mold and die maintained their original shapes at the baking temperature (50°C) as this temperature was below the glass transition temperature of the PLA (55 – 70°C)^[46,47]. Next, to separate the three parts (i.e., mold, cured Ecoflex, and die), they were immersed in acetone for 12 h to delaminate the PLA (**Figure 3E**)^[48], and subsequently, they were easily separated by hand

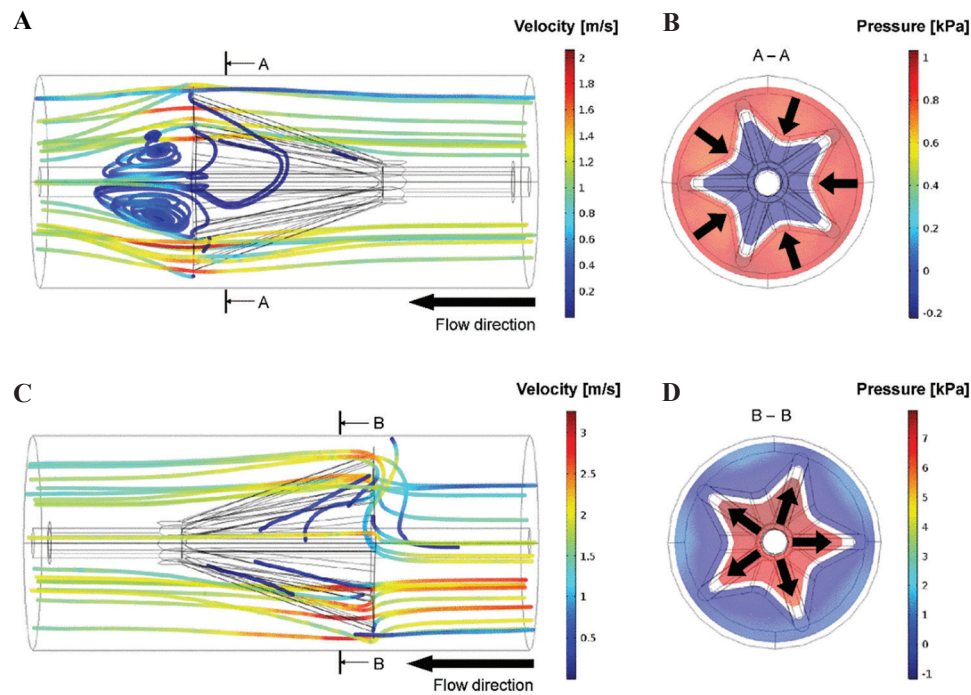


Figure 2. Simulation results for the penta-shaped extraluminal anti-reflux diode (EAD) under initial pressures of 18 cm-H₂O (1765 Pa) and 50 cm-H₂O (4903 Pa) for forward and backward directions, respectively. (A) Streamline in the forward direction. (B) Cross-section of pressure distribution in the forward direction. (C) Streamline in the backward direction. (D) Cross-section of pressure distribution in the backward direction.

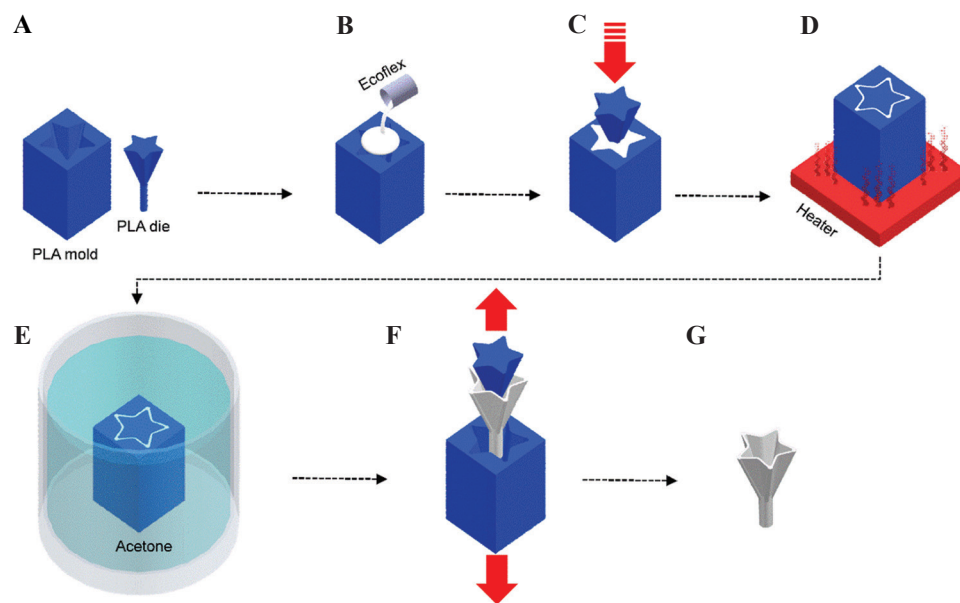


Figure 3. Schematic of the entire fabrication process. (A) Printing of the polylactic acid (PLA) mold and die using a 3D printer; (B) pouring of the Ecoflex onto the printed PLA mold; (C) pressing of the die into the mold after degassing process; (D) baking on a heater to cure the Ecoflex; (E) delamination of the PLA to separate the cured Ecoflex from the mold and die by immersing in acetone; (F) separation of the Ecoflex by hand; and (G) finalization of the fabrication of the extraluminal anti-reflux diode.

(Figure 3F). Finally, various types of anti-reflux devices were created (Figure 3G).

Figure 4 shows the optical and scanning electron microscopy (SEM) images of each manufactured EAD

and integrated with the DJ stent. The fabricated EADs can be divided into three parts (rib, canopy, and joining part), as shown in Figures 4A1 and A2. The rib parts prevent the EAD from being turned inside out, similar

to the ribs of an umbrella. The canopy parts (i.e., flexible membranes) can expand their shapes against the fluidic resistance during the reflux, which are similar to fabric panels of an umbrella. Furthermore, the joining parts allow the EAD to be assembled with the DJ stent. The optical images of the cross-sectional area of each type of EAD, i.e., quadra, penta, hexa, and octa, are presented in **Figures 4A1, B1, C1, and D1**, respectively. The rib and canopy thickness of each device were set to 1 and 0.4 mm, respectively, on CAD software. Because the rib is slightly thicker than the canopy, the device can avoid rollover (overturn) during the reflux. **Figures 4A2, B2, C2, and D2** show each standing EAD with a length of 2 cm. The length, inner diameter, and thickness of the joining part were 5, 1.8, and 0.4 mm, respectively. In this study, a DJ stent (6Fr, 22 cm, C. R. Bard Inc.) with a 2-mm outer diameter was used. Since the inner diameter of the joining part is slightly smaller than the outer diameter of the DJ stent, the EADs can be assembled mechanically with the DJ stent through press fit. **Figures 4A3, B3, C3, and D3** present the SEM images of the outer walls of each EAD with detailed rough surfaces. It should be noted that the uniform rough patterns of each EAD were formed due to the layer-by-layer printed mold. Furthermore, because the

printed PLA die was printed layer-by-layer, the inner wall of each EAD also had the same rough surface. **Figure 4E** shows a combination of the penta-shaped EAD and the DJ stent. Before the EAD and the DJ stent were assembled, they were placed in water for 5 min to allow for the mechanical friction of the joining part of the EAD to be reduced during the hand assembly that may induce cracks or rupture in the EAD. Therefore, the EAD can be located in the desired positions along the DJ stent without damage. In this study, we demonstrated the anti-reflux efficiency of each fabricated EAD using an experimental model. To investigate the best reflux prevention performance, parameters such as the shape of EAD, attaching position, and the number of attached devices were considered. Since the EAD and the DJ stent are assembled mechanically, the surface feature (roughness) is also important to decide attachment forces. Therefore, we utilized rough surfaces with patterns, which were formed by layer-by-layer deposition and compared them with smooth surfaces without patterns. Finally, to further demonstrate the safety and durability of EADs in the urine, surface deformation and chemical structure changes of EADs were observed using artificial urine.

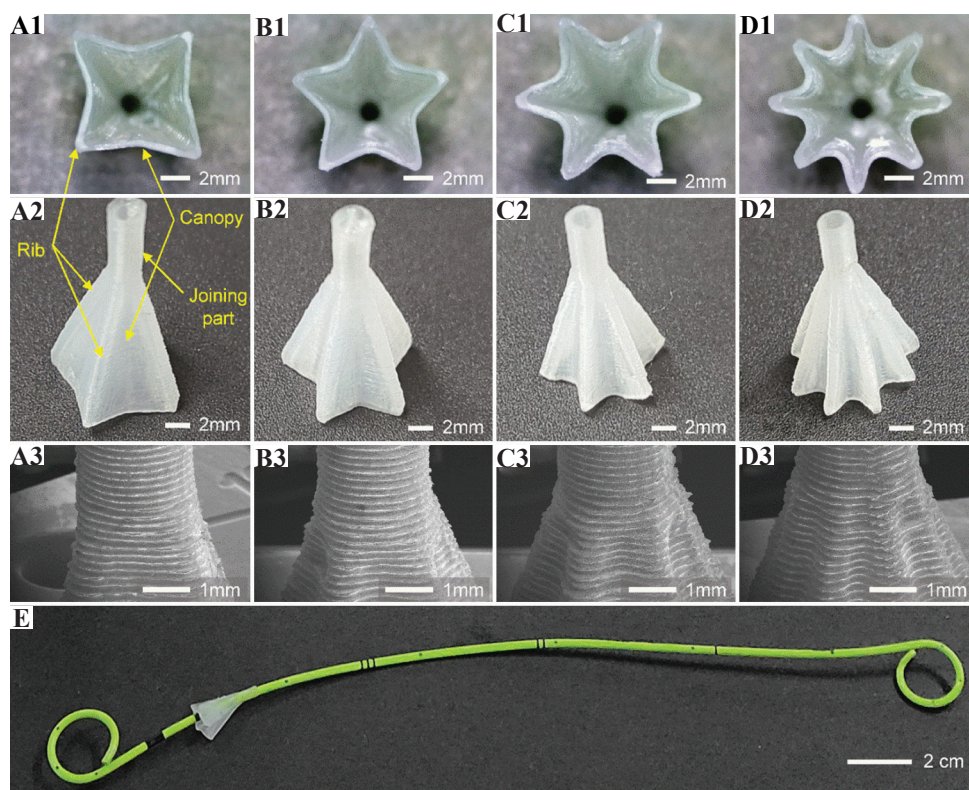


Figure 4. Optical images of cross-section of extraluminal anti-reflux diodes (EADs) with four different shapes: (A1) quadra, (B1) penta, (C1) hexa, and (D1) octa. Optical images of the standing EADs: (A2) quadra, (B2) penta, (C2) hexa, and (D2) octa. Tilted view of scanning electron microscopy images of each EAD: (A3) quadra, (B3) penta, (C3) hexa, and (D3) octa. (E) Optical image of the EAD integrated with the DJ stent.

3. Results and discussion

3.1. Anti-reflux performance

Figure 5 presents an experimental setup to characterize the anti-reflux performance of the EAD. To demonstrate and compare the anti-reflux performance of each EAD, a voiding (urination) model, which is designed for urination and reflux circumstances, was prepared using a 3D printer, transparent polycarbonate (PC) pipes, and silicone rubber. The designed voiding model is classified into three parts: 3D-printed bladder part where urine flows by urination pressure, urethra line in the bladder where urine is secreted, and ureter line where the reflux occurs along the inserted DJ stent. The bladder model was printed to have three different holes: 7-mm inner diameter for the urethra line, 10-mm inner diameter for the connection of the ureter line, and 30-mm inner diameter for 50-cm long PC pipe to provide the 50 cm-H₂O hydrostatic pressure and urine, as shown in **Figure 5A**. The bladder model and ureter line were connected using silicone rubber with a 10-mm inner diameter. To mimic the bladder pressure and urine simultaneously, hydrostatic pressure (i.e., 50 cm-H₂O) was used in this study^[21]. The PC pipe was filled with deionized water dyed in red color up to a length of 50 cm and assembled with the bladder model. Although water was filled in the PC pipe up to the 50-cm height to represent voiding pressure, the actual initial pressure was 48 cm-H₂O because some portion of the inner volume of the bladder model was filled with water in this experiment. The water flowed into the urethra and the ureter due to reflux when the stop valve was removed to apply pressure on the bladder model. Using this experimental model, in vitro experiments were conducted to determine

the efficiency of EADs of various shapes, which were inserted into the ureter after being assembled with the DJ stent. **Figure 5B** shows the urination state with reflux when the stop valve was removed. It was noticed that the canopy membrane of the EAD was expanded by the reflux pressure compared to normal EAD. This result is consistent with the simulation result (**Figure 2D**). The maximum height (indicated as $H_{\max}$ in **Figure 5B**) at which the reflux urine can rise in the ureter differs in response to the anti-reflux performance. Therefore, the efficiency of anti-reflux was characterized by measuring the maximum reflux height ($H_{\max}$) of the water along the ureter line when pressure was applied. The lower the $H_{\max}$ measured, the better the anti-reflux efficiency.

Figure 6A shows the measured $H_{\max}$ with respect to the types of EADs and attached positions along the DJ stent using a urination model. The positions are presented in **Figures 6B–D**, and only one device was attached to the DJ stent during this experiment. Five types (without EAD and with quadra-, penta-, hexa-, and octa-shaped EADs) of a single device were evaluated 5 times with respect to each position (Position #1, Position #2, and Position #3). Accordingly, the penta-shaped EAD exhibited the best anti-reflux performance at Position #1 ($H_{\max}$ = 220.6 mm) with a 44% decrease in the maximum reflux height compared to that without EAD ($H_{\max}$ = 394 mm). Moreover, the penta-shaped device showed the best efficiency compared to the other types of EADs at the same attached position along the DJ stent, as shown in **Figure 6A**. Thus, the penta-shaped EAD was beneficial in significantly mitigating the urine reflux in this study. It was noticed that the anti-reflux efficiency of the devices showed the same tendency at each attached position. The efficiency decreased in the order of penta-, octa-, hexa-

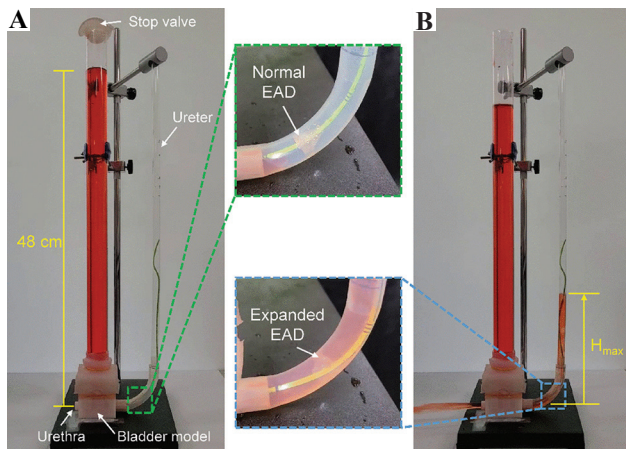


Figure 5. Experimental setup to characterize the anti-reflux efficiency. (A) Urination model with the extraluminal anti-reflux diode (EAD) and the DJ stent before the bladder pressure was applied with the zoomed-in image of normal EAD. (B) Urination state after the removal of the stop valve with the zoomed-in image of expanded EAD. Maximum height in the backflow ($H_{\max}$) can be varied in response to the anti-reflux efficiency.

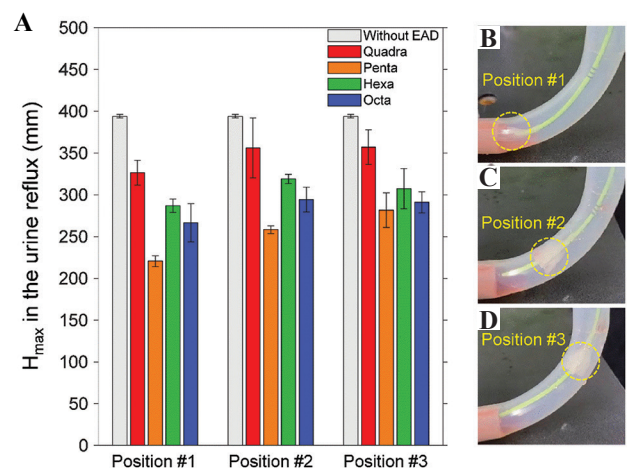


Figure 6. (A) Average values of the maximum height in the urine reflux without and with four different types of extraluminal anti-reflux diodes (quadra-, penta-, hexa-, and octa-shaped) with respect to the attached position along the DJ stent. (B) Position #1, (C) Position #2, and (D) Position #3.

, and quadra-shaped EADs. This tendency can possibly be attributed to the difference in the internal area, where urine can flow during the reflux. When the internal areas of each EAD were measured using the CAD model, the penta-, quadra-, octa-, and hexa-shaped EADs showed areas of 46.53, 46.01, 45.94, and 44.94 mm², respectively. As the internal area increased, the EAD has the potential to be expanded because more urine flow can be trapped inside the EAD when initial reflux occurs. In addition, the external area (i.e., the spatial area between the expanded EAD wall and the inner wall of the ureter) will decrease as the internal area of EAD increases, thus increasing the flow resistance in the ureter, which results in reduced $H_{\max}$. Although the internal area of the quadra-shaped EAD is larger than that of the hexa- and octa-shaped EADs, its anti-reflux efficiency is lower than that of the others. Here, the quadra-shaped EAD was flipped (overturned) during the reflux because the number of ribs was not enough to maintain the overall shape against reflex pressure. Therefore, the quadra-shaped EAD showed the worst anti-reflux efficiency in this study.

To further characterize the anti-reflux effectiveness with respect to the number of attached EADs, an experiment was performed using an increasing number of penta-shaped EADs, which exhibited the best performance in the previous experiments. **Figures 7A-C** show the number of attached EADs (single, double, and triple) at the various positions. The joining part of the EAD was located close to the side hole of the DJ stent to avoid covering the side hole, and then the position was determined. Due to the unequal distance between the side holes, the distance between the positions also differed slightly. The distances between Positions #1 and #2 and Positions #2 and #3 were 17.5 and 22 mm, respectively, as shown in **Figures 7B and C**. Four experimental conditions (without EAD and with single, double, and triple penta-shaped EADs) were tested 5 times for each

case. Consequently, the average values of $H_{\max}$ were measured to be 394, 220.6, 223.2, and 228.8 mm for the DJ stent without EAD and with single, double, and triple penta-shaped EADs, respectively, as shown in **Figure 7D**. The results showed that no significant variations existed in $H_{\max}$ between the single, double, and triple EADs. This might be because the pressure gradient, which helps the EAD expand, was significantly decreased across the EAD at Position #1. Due to the decreased pressure gradient, the subsequent EADs (i.e., EADs at Positions #2 and #3) did not fully expand to sufficiently block the ureter line. Thus, water flowed in the external area, and the EADs at Positions #2 or #3 may not work. This also indicated that a single EAD attached at Position #1 (near the VUJ) sufficed to mitigate urine reflux in the ureter line. From the results shown in **Figures 6 and 7**, a single penta-shaped EAD at Position #1 had the best performance in preventing reflux, and the anti-reflux performance did not change significantly depending on the number of attached EADs. In summary, the device with the highest effectiveness and least irritation to patients was found to be a single penta-shaped EAD at Position #1 in this study.

Table 1 shows a comparison of anti-reflex devices between this study and previous literature to reduce the VUR. It was noteworthy that previous studies have focused on intraluminal reflux issues whereas this study developed the anti-reflux device to prevent the extraluminal reflux. In addition, because the material used in this study (i.e., Ecoflex) is inherently biocompatible^[44,45], additional processes such as parylene C coating were not required on the anti-reflex devices to enhance the biocompatibility. To characterize the anti-reflux performance, flow rate under the driven pressure was measured through the intraluminal anti-reflux devices. However, because urine can reach the renal pelvis for a long time and the pressure was continuously supplied during experiments^[21,23], these methods could

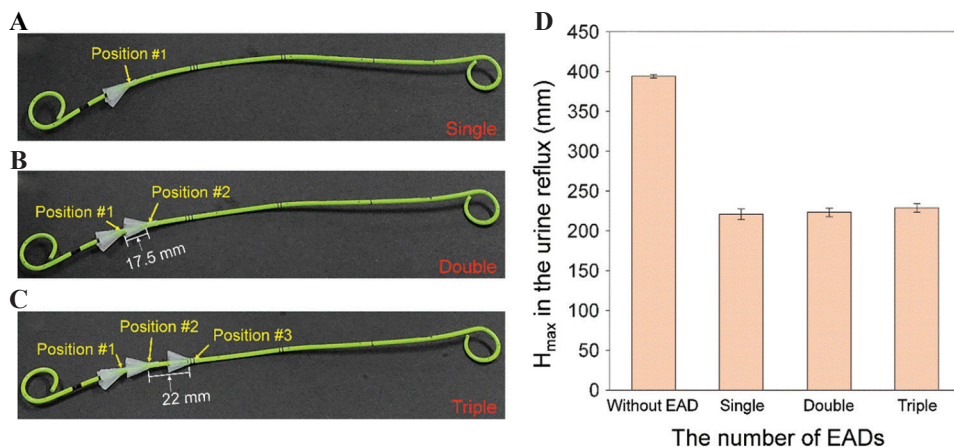


Figure 7. DJ stent assembled with (A) single penta-shaped extraluminal anti-reflux diode (EAD) at Position #1, (B) double penta-shaped EADs at Positions #1 and #2, and (C) triple penta-shaped EADs at Positions #1, #2, and #3. (D) Average values of maximum height in the urine reflux with respect to the number of EADs.

not present suitable voiding situations compared to this study. Nonetheless, to demonstrate the use of the EAD in the human body, further *in vivo* or clinical trial studies are needed. Although intraluminal reflux was not considered in this study, various intraluminal anti-reflux devices have been demonstrated and cone-shaped anti-reflux devices are commercially available^[15]. When the EAD is combined with these intraluminal anti-reflux devices, the overall efficiency of reflux prevention alongside the stents will be dramatically increased. Consequently, patients are expected to be free from the urological complications caused by the VUR.

3.2. Mechanical adhesion and friction test

It is important to avoid easy separation (disassembly) of the EAD from the DJ stent during insertion into the ureter line. Because of the features of the FDM-printing method, a rough surface with regular patterns appeared both inside and outside the joining part, as shown in **Figures 4A3, B3, C3, and D3**. In this work, we utilized these unique patterns of the joining parts for stable and robust mechanical bonding with the DJ stent by enhancing the friction effect. To demonstrate the benefit of a rough surface, the tensile (pulling) load at the interface between the joining part and stent surface was measured using a tensile testing machine (MCT-2150, A&D Co.). To investigate the effect of the patterned surface, two types of specimens were prepared, that is, with and without patterned rough surfaces of the joining part; these specimens had a length, inner diameter, and thickness of 5, 1.8, and 0.4 mm, respectively. Casting fabrication methods (**Figure 3**) were also used in fabricating the specimens with and without a rough surface. In this study, an acrylonitrile butadiene styrene (ABS) filament was used to create the joining part without patterns. Since ABS melts in acetone, the rough surface of the ABS die was polished by acetone while maintaining the same diameter of the PLA die (**Figure S1** in Supplementary File). After assembly with the DJ stent, adhesion forces were measured by holding the DJ stent and pulling it at a speed of 50 mm/min and up to a displacement of 40 mm using a tensile testing machine (**Figure S2** in Supplementary File). In this experiment, three different specimens for each joining part with and

without patterns were prepared and evaluated to measure the adhesion forces.

Figure 8A shows the measured tensile load (i.e., adhesion force) of each specimen with respect to the displacement at a pulling speed of 50 mm/min. Consequently, the characteristics of surface types (with and without patterns) were distinctly divided into “slip” and “miss” behaviors. For the joining part with rough patterns, the joining part was well attached on the surface of the DJ stent up to the pulling displacement of 20 – 25 mm, as confirmed from the linearly increased load. When the pulling displacement exceeded 25 mm, the measured load gradually decreased, meaning the joining part started slipping from the surface of the stent. In contrast, the joining part without rough patterns showed a relatively low load and a sudden drop in pulling load near a pulling displacement of 25 mm. This indicated that the joining part was suddenly separated (missed) from the stent. The joining part without rough patterns was also torn before separation from the DJ stent. Thus, a smooth surface is more dangerous because the EAD can be broken away from the stent during insertion. In summary, this result implies that the rough surface with patterns formed by FDM printing exhibited relatively durable adhesion and longer attaching time with the DJ stent than the smooth surface without patterns.

Figure 8B shows the average maximum load for the joining parts with rough and smooth surfaces. Consequently, specimens with and without surface patterns showed maximum tensile loads of 1274.4 and 1005.6 mN, respectively. The maximum average load of the rough surface with patterns was 26.7% higher than that of the smooth surface without patterns. A higher maximum load might be caused by the water (or urine) between the grooved patterns and the surface of the stent. The frictional force increased with the contact area when the same normal pressure was applied. Therefore, the applied load of a specimen with a smooth surface was assumed to be larger than that of a rough surface. However, if water is present between the smooth surface and the surface of the DJ stent, the actual contact area at the interface significantly decreases due to the thin liquid film, thus considerably reducing the frictional stress. In

Table 1. Comparison of the anti-reflux devices

Reflux type	Material	Dimensions	Method	Measurement	Ref.
Intraluminal	Polyurethane	N/A	Clinical trial	Questionnaire	[15]
Intraluminal	Tango Plus with parylene C coating	2.8 mm×5.3 mm	In vitro	Flow rate	[21]
Intraluminal	Silicone sleeve	15 mm×26 mm	In vitro/ Clinical trial	Flow rate/ Cystogram	[23]
Intraluminal	Tango Plus with parylene C coating	2.8 mm×5.3 mm	In vivo	VUR grade	[25]
Intraluminal	Polyurethane with hydrogel coating	N/A	Clinical trial	Questionnaire	[27]
Extraluminal	Ecoflex	10 mm × 20 mm	In vitro	Reflux height	This work

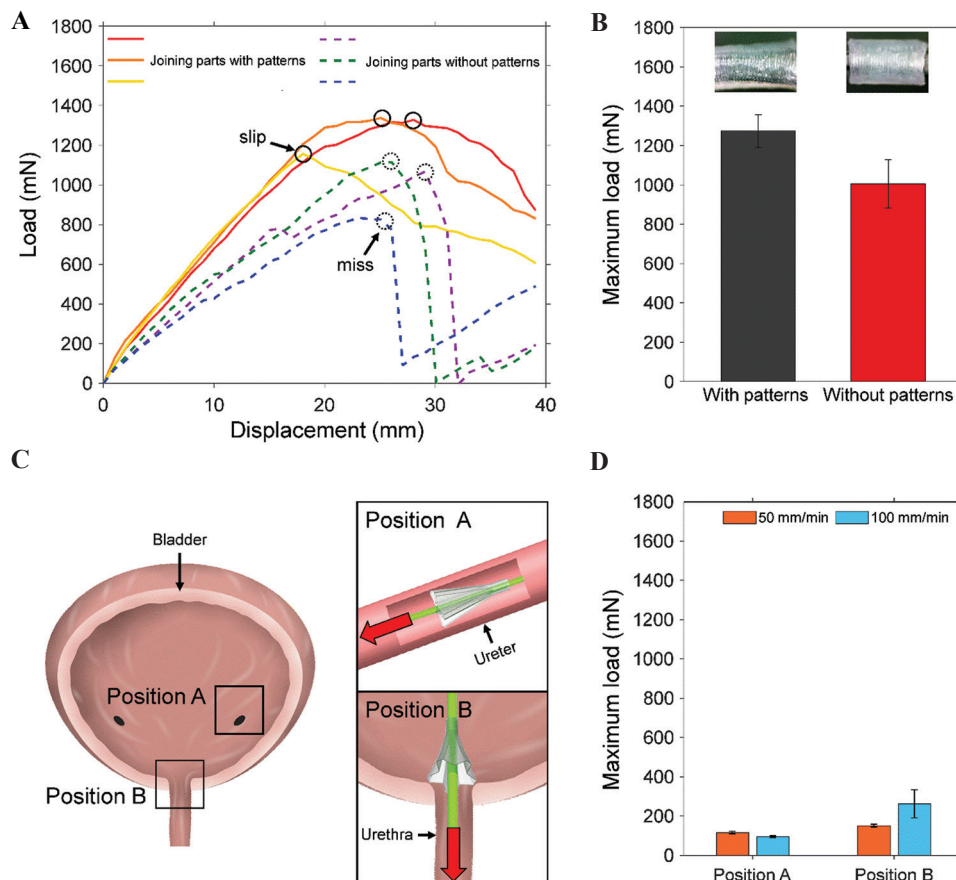


Figure 8. Mechanical properties of the extraluminal anti-reflux diode (EAD) with the DJ stent during insertion and removal. (A and B) Adhesion forces of joining parts with the DJ stent with a pulling speed of 50 mm/min. Comparison between rough surface (with patterns) and smooth surface (without patterns). (A) Applied load of specimens with respect to displacement. (B) Maximum average load of each joining part. Inset: inner surface of the joining parts (with and without patterns). (C) Schematic illustration of removal of the DJ stent with respect to the positions. Position A is path where the EAD is removing from the ureter to the bladder. Position B is path where the EAD is removing from the bladder to the urethra. (D) Friction forces between the EAD and silicone rubber with pulling speeds of 50 and 100 mm/min. Maximum average load at each position with respect to the pulling speed.

contrast, at the interface between grooved patterns and the surface of the stent, the water can be trapped in the grooved patterns, and the tips of the grooved patterns can still contact the stent surface, leading to an increase in friction^[49]. This may lead to a higher maximum load of friction in a rough surface with patterns than a smooth surface without patterns. Taken together, the EAD with the patterned joining part is more beneficial for strong adhesion to the DJ stent compared to that with the joining part without patterns when the stent is inserting into the ureter. Based on this experiment, it was confirmed that a rough surface with patterns is more advantageous for mechanical coupling between the EAD and DJ stent. Hence, the disadvantage (rough surface) of the FDM-type 3D printer was utilized as a beneficial property in this study.

To use the EAD to the patients in practical, the ureter should not be injured when clinicians remove the DJ stents. For this reason, a friction test was additionally

conducted to demonstrate that the EAD does not damage the ureteral mucosa during the removal of DJ stent. While removing the DJ stent, the EAD passes through ureter, bladder, and urethra, successively. In this study, friction forces between the EAD and silicone rubber, which emulate urinary organs (i.e., ureter and urethra) wall, were measured using in vitro experiment. **Figure 8C** shows the Positions A and B that represent different moving paths from the ureter to the bladder and from the bladder to the urethra, respectively. Positions A and B were implemented in the experimental setup, as shown in **Figure S3** in Supplementary File. Because the EAD is fully surrounded by the ureter at Position A during removal, silicone rubber covered whole EAD, as shown in **Figures S3A1 and A2**. To mimic the removal through Position B, the EAD was initially placed outside of silicone rubber (i.e., bladder) and pulled back through silicone rubber (i.e., urethra), as shown in **Figures S3B1 and B2**. It was noteworthy that the EAD was flipped over when

the DJ stent was pulled from the outside to the inside of silicone rubber, as shown in **Figure S3B2**. Friction forces for each case were measured by pulling the DJ stent up along a displacement of 40 mm using a tensile testing machine. The experiments were conducted with pulling speeds of 50 and 100 mm/min, and repeated 3 times.

Figure 8D shows the averaged maximum load between the EAD and inner wall of silicone rubber with respect to Positions A and B. Position A showed maximum tensile load 116.65 and 96.04 mN at a pulling speed of 50 and 100 mm/min, respectively. Position B showed maximum tensile load 157.74 and 263.34 mN at a pulling speed of 50 and 100 mm/min, respectively. Although the friction forces were present during the removal of DJ stent, these forces were considerably lower than the threshold force that can injure the inner wall of the ureter (2.9 N)^[50]. The averaged maximum load at Position B showed higher values than those at Position A, but still negligible compared to the threshold force of 2.9 N. This was because more load was required to flip the EAD at Position B, thus increasing the friction force simultaneously. However, it was noteworthy that once the EAD was flipped, the EAD was easily removed in the silicone rubber with lower friction forces. Consequently, the fabricated EAD is expected not to damage or injure the inner wall (mucosa) of the ureter and urethra during both insertion and removal operations.

3.3. Safety and durability test in urine

To investigate the safety and durability of EADs made of Ecoflex (biocompatible) materials, the changes in the surface and chemical structure of the EADs were thoroughly examined in four types of artificial urine (Biozoo Biological Supply Co.): low-pH, normal-pH, high-pH, and glucose urine. The chemical composition

of each artificial urine sample is presented in **Table 2**. For the long-term experiment, the penta-shaped EADs were immersed in each artificial urine sample in a vial and kept in a water bath at 36.5°C (body temperature) for 4 weeks. After 4 weeks, the EADs were washed with deionized (DI) water to investigate whether the EAD was physically damaged or chemically corroded by urine. **Figures 9A1, B1, C1, and D1** show the SEM images of the EADs surface washed after immersion in low-pH, normal-pH, high-pH, and glucose urine, respectively. No physical damage or solidified residues of urine were observed after rinsing with DI water. This characteristic is clearly distinct from the surfaces of the unwashed EADs. **Figures 9A2, B2, C2, and D2** show SEM images of the surfaces of unwashed EADs after immersion in low-pH, normal-pH, high-pH, and glucose urine for 4 weeks, respectively. Each unwashed EAD was dried at 36.5°C for 12 h without being rinsed with deionized water. The surfaces of the unwashed EADs showed adhered urinary stones for EADs immersed in low-pH, normal-pH, and high-pH urine, and solidified glucose residues for the EAD immersed in glucose urine. These results imply that the washing process can remove residues of urine effectively, and thus the EADs are reusable without physical damage after being washed with water.

To further demonstrate the chemically stable structures of the EADs in urine, FTIR (Nicolet iS50, Thermo Fisher Scientific Inc.) analysis was performed, as shown in **Figure 10**. The absorbance with respect to the wavenumber was measured to compare the chemical structures of the EADs before and after immersion in artificial urine. For the bare EAD before immersion in urine, the absorbance bands were observed at wavenumbers of 2963, 1260, 1089, 1018, and

Table 2. Chemical composition and pH of artificial low-pH, normal-pH, high-pH, and glucose urine

Ingredients (g/L)	Artificial urine type			
	Low-pH (pH 5)	Normal-pH (pH 7)	High-pH (pH 9)	Glucose (pH 7)
Calcium Chloride	0.49	0.49	0.49	0.49
Magnesium Chloride	0.3	0.3	0.3	0.3
Potassium Chloride	1.6	1.6	1.6	1.6
Potassium Phosphate	2.8	2.8	2.8	2.8
Ammonium Chloride	1.0	1.0	1.0	1.0
Sodium Sulfate	2.3	2.3	2.3	2.3
Sodium Chloride	2.5	2.5	2.5	2.5
Urea	2.5	2.5	2.5	2.5
Creatine	1.1	1.1	1.1	1.1
Sodium Hydroxide	1.0	-	1.0	-
Potassium Biphthalate	10	-	-	-
Boric Acid	-	-	3.0	-
Glucose	-	-	-	0.5

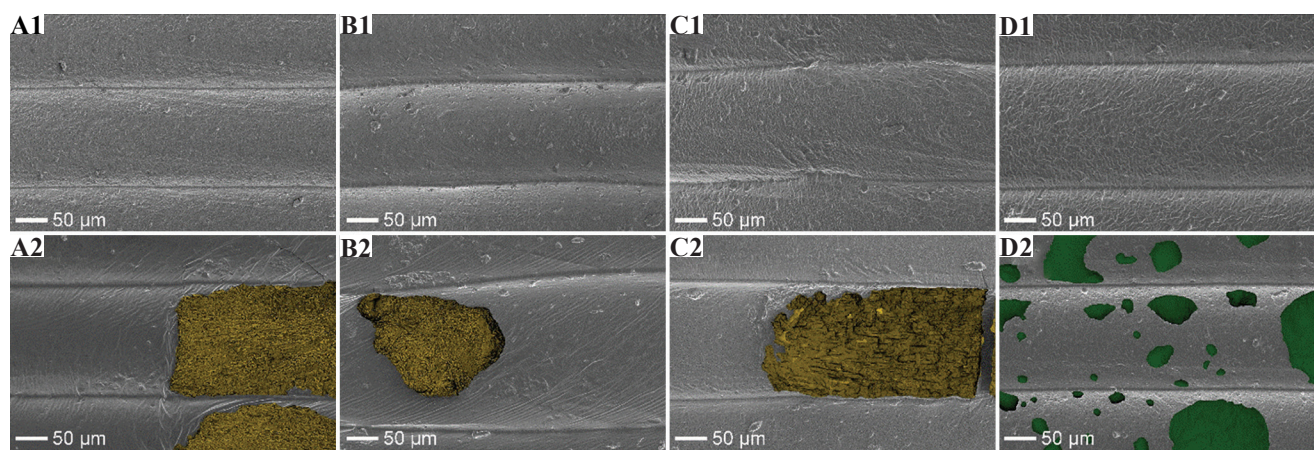


Figure 9. SEM images of the surfaces of extraluminal anti-reflux diodes immersed in artificial urine for 4 weeks. The surface rinsed using DI water after immersing in artificial (A1) low-pH, (B1) normal-pH, (C1) high-pH, and (D1) glucose urine. The unwashed surface after immersion in artificial (A2) low-pH, (B2) normal-pH, (C2) high-pH, and (D2) glucose urine. (A2), (B2), (C2) Urinary stones are overlaid with yellow color for visualization. (D2) Solidified glucose residues are overlaid with green color for visualization.

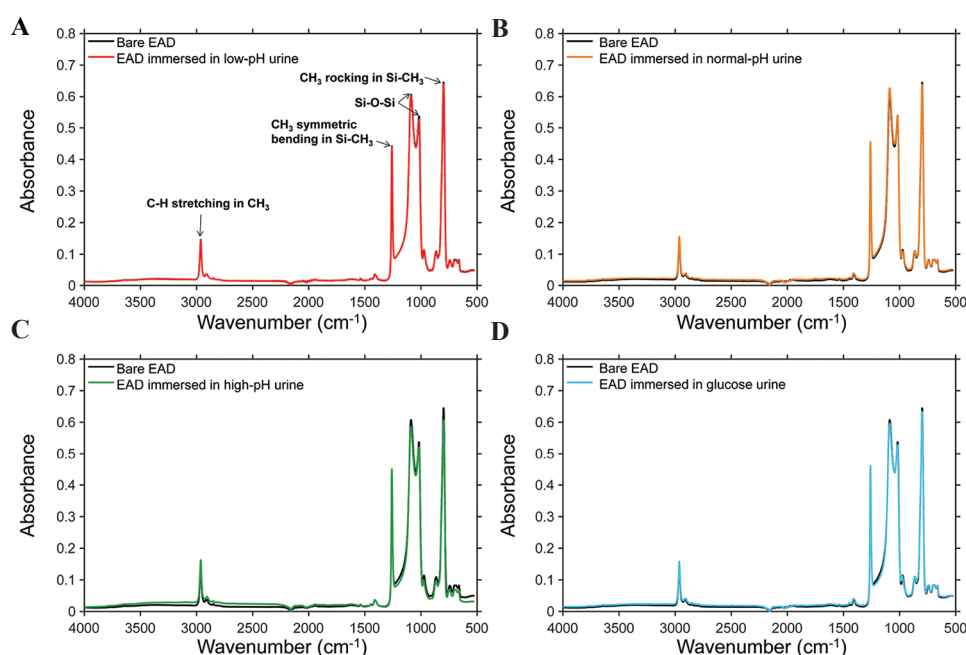


Figure 10. FTIR spectra of extraluminal anti-reflux diodes before and after immersion in (A) low-pH urine, (B) normal-pH urine, (C) high-pH urine, and (d) glucose urine for 4 weeks.

799.8 cm^{-1} , which represented C-H stretching in CH_3 , CH_3 symmetrical bending in Si-CH_3 , asymmetric stretching of Si-O-Si , symmetric stretching of Si-O-Si , and CH_3 rocking in Si-CH_3 , respectively^[51,52]. The FTIR peaks of the absorbance bands exactly overlapped with those of the EADs immersed in low-pH, normal-pH, high-pH, and glucose urine, as shown in **Figures 10A, B, C, and D**, respectively. This implied that the chemical structures of the Ecoflex EADs were not affected by urine^[53]. These results also demonstrated that the fabricated EADs were mechanically and chemically stable, even after long-term soaking in urine. Therefore, it is noteworthy that the

EADs are mechanically and chemically safe in the ureter line and reusable as long as they are washed with water.

4. Conclusion

In this study, anti-reflux devices based on an umbrella shape and with a DJ stent were successfully fabricated and demonstrated to prevent VUR and provide facile drainage. The working mechanisms are based on the change in the internal area of the EAD as it deforms under fluid pressure. To estimate the feasibility of the rectification performance through the EAD, a

computational simulation was conducted for forward and backward urine flows. Consequently, the difference in the cross-sectional pressure fields of the penta-shaped EAD could expand the canopy membrane along the rib structures of the EAD. For the fabrication of the EADs, 3D printing and casting methods were utilized. The printed PLA mold and die were tailored to create four different umbrella shapes with flexible and biocompatible Ecoflex. Among the fabricated devices, the penta-shaped EAD showed the best anti-reflux performance compared to the other types. The maximum anti-reflux efficiency was observed when the EAD was attached near the bladder-ureter junction, and an approximately 44% decrease in reflux was demonstrated in the ureter line using a voiding model. In addition, the anti-reflux efficiency did not show significant changes depending on the number of EADs attached to the DJ stent. Thus, a single EAD sufficed to minimize reflux of urine with minimal discomfort to patients. A disadvantage of the FDM-type 3D printer (i.e., rough surface with grooved patterns) was intentionally used for mechanically robust adhesion between the EAD and DJ stent. Finally, a long-term soaking test in artificial urine with different pH values was performed to demonstrate the safety, mechanical durability, and chemical stability of the device in urine for at least 4 weeks. Although *in vivo* and parametric studies on the length, shape, and thickness of the EAD are required to enhance the rectification performance, the findings of this study support the use of 3D printing methods to manufacture various medical devices with flexibility, biocompatibility, mechanical durability, and chemical stability for urological applications.

Funding

This work was supported by the National Research Foundation of Korea (NRF), funded by the Ministry of Science and ICT of the Republic of Korea (No. NRF-2021R1C1C1010836).

Conflict of interest

The authors declare that there is no conflict of interest.

Author contributions

J. L. Conceptualization, methodology, formal analysis, investigation, data curation, validation, visualization, writing - original draft, writing - review and editing. J. S. Conceptualization, methodology, investigation, data curation, validation, writing - review and editing. J. K. J. Conceptualization, methodology, formal analysis, investigation, supervision, writing - review and editing. H. S. Conceptualization, methodology, resources, supervision, writing - review and editing, funding acquisition.

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