Review Article

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Novel Clinical Therapies and Technologies in Dialysis Vascular Access

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Abstract

The hemodialysis population continues to grow. Although procedures for dialysis have existed for >60 years, significant challenges with vascular access to support hemodialysis persist. Failure of arteriovenous fistulas (AVFs) to mature, loss of AVF and graft patency, thrombosis, and infection hinder long-term access, and add extra health care costs and patient morbidity. There have been numerous innovations over the last decade aimed at addressing the issues. In this study, we review the literature and summarize the recent evolution of drug delivery, graft development, minimally invasive AVF creation, and stem-cell therapy for hemodialysis access.

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Introduction

There are approximately 4 million patients worldwide with ESKD (1). Many of these patients will require a well-functioning vascular access so hemodialysis can be performed. The surgically placed arteriovenous fistula (AVF) has been the preferred modality for several decades but has limited long-term patency (2). As a result, much effort has been spent on improving AVF patency through innovative technologies and alternative vascular access development.

Dialysis access creation and maintenance is continually evolving. In 1966, Cimino and colleagues reported the first surgically created radiocephalic AVF for intermittent hemodialysis (3). This gradually replaced the prior Quinton–Scribner Teflon-based shunt. Since then, many attempts have been made to improve the durability and function of the AVF. However, sustaining long-term AVF patency remains a challenge (4). Drug-coated balloons (DCBs) may help maintain satisfactory vascular access, whereas stem-cell therapy and alternative drug delivery methods may improve the success of fistula maturation. Grafts are the second-line modality for access. Although the expanded polytetrafluoroethylene (ePTFE) graft remains the standard for graft construction, new graft devices and materials are being studied. This goal of this paper is to review some of the recent technologies that may improve or prolong vascular access for hemodialysis including DCBs, newer graft designs, endovascular AVF (endoAVF) creation, stem-cell applications, and new alternative drug therapies.

Grafts

Dialysis grafts are second line to dialysis fistulas due to higher rates of infection, neointimal hyperplasia at the venous anastomosis, and thrombosis (5,6). However, grafts mature faster and can be used in patients with diminutive veins that cannot support fistula creation (7,8). In general, ePTFE dialysis grafts should not be cannulated until swelling has improved enough to allow palpation of the graft, which usually takes about 3–6 weeks (7). In contrast, dialysis AVFs typically require 1–4 months for the vein to dilate enough to sustain adequate blood flow and enable palpation for access (9). There have been several innovations in graft technology in recent years to offer benefits over fistulas and address the shortcomings of tradition grafts.

Bioengineered Grafts

Bioengineered grafts are another potential modality to address the issues encountered with ePTFE grafts. In patients with coronary or peripheral artery disease, autologous vessels are preferred over synthetic grafts due to better patency. Therefore, dialysis grafts constructed from a patient's own tissue may have improved patency. Attempts at creating bioengineered vascular tissue date back to 1948, with canine aortic transplant experiments (10).

More recently, studies have investigated the feasibility of using *in vitro* bioengineered hemodialysis grafts. A multicenter study enrolled ten patients with ESKD to receive completely autologous tissue-engineered grafts for hemodialysis (11). Although most grafts were able to be used for dialysis, the primary patency was 60% at 6 months and three grafts failed in the first 3 months.

Subsequently, Lawson and colleagues showed human acellular vessels cultured *in vitro* using human vascular smooth muscle cells on a biodegradable scaffold created a potentially viable dialysis conduit (12). The acellular vessels were placed in 60 patients with a mean follow-up time of 16 months. Although only one vessel developed infection, patency was limited. The 1-year primary patency, primary assisted patency, and secondary patency were 28%, 38%, and 89%, respectively. Furthermore, 155 procedures were

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performed, mostly to maintain patency of the 60 grafts. Thus, these patency issues need to be addressed before bioengineered graft can be adopted for routine implantation.

Hemodialysis Reliable Outflow Graft

The Hemodialysis Reliable Outflow (HeRO) graft (Merit Medical, South Jordan, UT) was designed to address failing AVFs and AVGs in patients with central venous obstruction. The device comprises a 6 mm inner diameter ePTFE arterial graft component and a 5 mm inner diameter nitinol-reinforced silicone venous outflow component. The venous outflow component is placed into the internal jugular vein, and advanced until the radiopaque marker is in the mid- to upper-right atrium. The arterial graft is then tunneled from the brachial artery just proximal to the antecubital fossa, over the biceps muscle, to the deltopectoral groove. The graft is then attached to the outflow component using a titanium connector (Figure 1).

Cline *et al*. compared conversion of arteriovenous access to either a HeRO graft or central venous stent placement (13). The authors found that patients treated with HeRO graft conversions had superior primary and secondary patency rates at 6 and 12 months. The HeRO graft also has a low infection rate. In a study with 38 patients, the overall bacteremia rate was 1.71/1000 days, with a HeRO-related bacteremia rate of just 0.70/1000 days (14). The mean follow-up time in that study was 8.6 months.

InnAVasc Graft

The InnAVasc graft is a novel device that attempts to address many of the inadequacies in hemodialysis access. The graft has specific access chambers meant to prevent back or sidewall access. These cannulation zones have self-sealing technology to enable immediate use and eliminate the need for tissue incorporation (15). Although more data are needed on durability, thrombosis rates, and infection risk, the concept and initial experience are promising.

DCBs

The concept of local drug delivery via balloon angioplasty has existed for nearly 30 years (16,17). Initial trials were in animal models. However, it was not until recently that DCBs became approved by the Federal Drug Administration for clinical use in AVFs in the United States. Currently, the Lutonix and IN.PACT Admiral AV balloons are available for the treatment of AVF stenosis. With these DCBs, paclitaxel, an antiproliferative drug, is transferred to the vessel wall at the time of balloon inflation (Figure 2).

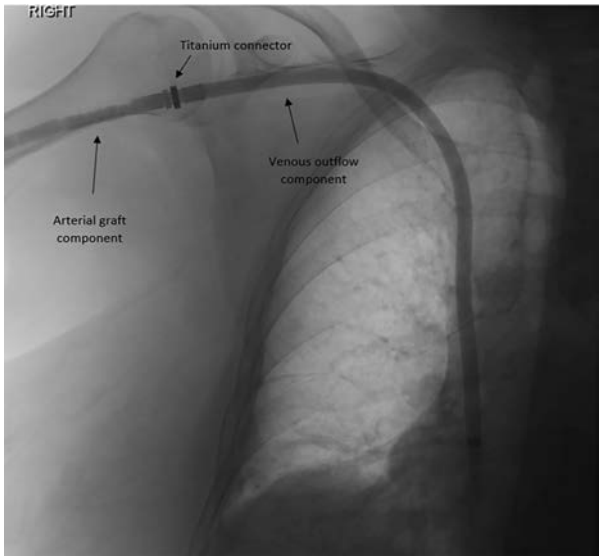

Figure 1. | **HeRo Graft.** Fistulogram demonstrating a patent HeRO graft with components labeled.

The Lutonix AV clinical trial, published in 2018, was a randomized controlled trial that enrolled 285 patients with dysfunctional AVFs (18). Patients who underwent plain angioplasty with a resultant ≤30% residual stenosis went on to receive further angioplasty with either a paclitaxel-coated balloon or a plain balloon control. The data showed no significant difference in the primary efficacy end point of target lesion primary patency at 6 months (71±4% for the DCB and 63±4% for control; $P=0.06$). Subsequently, the IN.PACT AV Access randomized trial showed DCBs were superior to high-pressure angioplasty through 6 months of follow-up (19). The authors reported the DCB group had a target-lesion primary patency of 82.2%

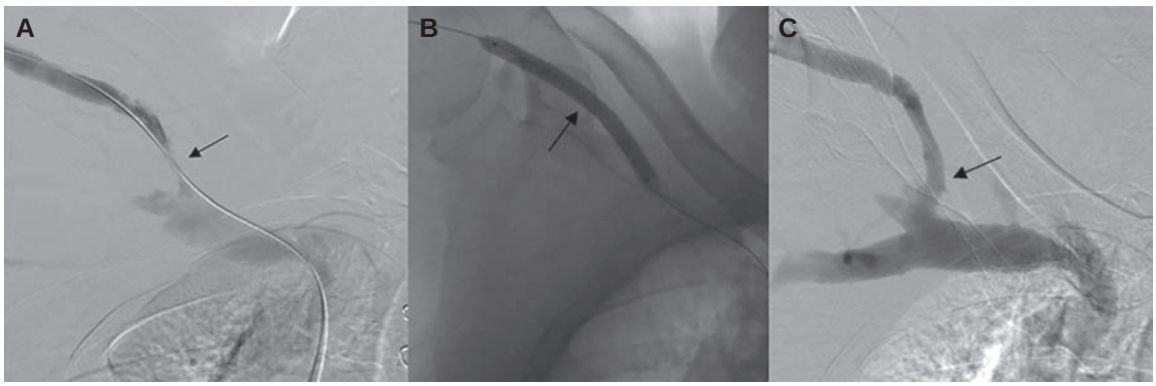

Figure 2. | **Drug-coated balloon angioplasty.** (A) 73-year-old male with high-grade cephalic arch stenosis (black arrow). (B) The stenosis was treated with DCB angioplasty (black arrow). (C) Repeat fistulogram immediately after angioplasty shows resolution of the stenosis (black arrow) and more robust contrast flow through the central veins. The fistula remained patent up to 19 months of available follow-up.

compared with approximately 59.5% in the high-pressure angioplasty group ($P<0.001$).

There is ongoing controversy over the safety of paclitaxel-coated balloons. A meta-analysis on paclitaxel-coated balloons and stents in lower extremity revascularization showed a significant increase in all-cause mortality (20). Subsequent studies have inconsistently confirmed those findings (21–24). A subgroup analysis of the Lutonix AV trial showed no significant difference in mortality in the DCB group compared with the control group (25).

Balloons coated with alternative drugs may be a solution to the paclitaxel mortality issue. The MAgicTouch Intervention Leap for Dialysis Access Trial was a single center, single-arm prospective pilot study investigating sirolimus-coated balloons for treating failing AVFs (26). Early data from the trial showed 82.9% target lesion primary patency at 6 months, which was superior to both the Lutonix AV and IN.PACT AV Access trials. There was a total of four (12.1%) deaths out to 8.7 months of follow-up, all related to cardiovascular comorbidities. The 1-year trial data are still pending.

EndoAVF Creation

Although surgically created AVFs are the ideal modality for hemodialysis access, they are still subject to issues with poor maturation, limited patency, and high intervention rates (27). A more minimally invasive method to construct AVFs may decrease vessel trauma and decrease procedure time, costs, and intimal hyperplasia (28,29). There are two devices available for endoAVF creation: the WavelinQ 4F EndoAVF System (Becton, Dickinson and Company, NJ, USA), formerly everlinQ before the Becton, Dickinson and Company acquisition of TVA Medical, and the Ellipsys Vascular Access System (Avenu Medical, San Juan Capistrano, CA, USA).

The WavelinQ EndoAVF device uses two catheters to create the AVF. One catheter is advanced through the brachial artery and a second into the brachial vein. When the catheters are aligned in the radial or ulnar artery and corresponding vein, magnets in each catheter attract one another and hold the two vessels together. Radiofrequency energy from the venous catheter then creates a channel between the two vessels. It is recommended that the brachial vein is embolized to promote maturation (Figure 3). The Ellipsys system uses a single catheter that is introduced through the deep communicating vein and advanced through the vein wall into the proximal radial artery. Using thermal energy and pressure, an anastomosis is created.

A technical success of ≥98% has been reported with either endoAVF device (29,30). In one study, the mean procedure time was just 15 minutes (31). A clinically functioning AVF to adequately support hemodialysis was achieved >95% of the time (32). The reported 1-year primary, primary assisted, and secondary patency rates with the Ellipsys system are 54%, 85%, and 96%, respectively (31). The cumulative patency with the WavelinQ system has been shown to be 92.8% after 1 year and 91.6% at 2 years (32). The costs related to managing AVF issues such as stenosis, thrombosis, and infection are lower among endoAVFs compared surgically created AVFs (28,33,34). Furthermore, patient satisfaction scores after endoAVF creation tend to be favorable (32). Thus, endoAVF techniques may offer a preferable vascular access option compared with surgically created AVFs, and potentially decrease patient morbidity not only at the time of creation, but in AVF maintenance as well.

Stem-cell Therapy

Stem cells can be isolated from the blood, fat, bone marrow, and other sources (35). They have been used in several different cardiovascular and peripheral arterial trials for reducing vascular injury due to inflammation, fibrosis, and hypoxic injury. Venous neointimal hyperplasia associated with hemodialysis vascular access is caused by trauma or changes in shear stress results in AVF stenosis and functional impairment (36). Thus, stem cells have a role for decreasing venous neointimal hyperplasia and reducing the need for invasive therapies for AVF maintenance.

Data on stem-cell applications in hemodialysis AVFs are limited. However, a recent study demonstrated that human adipose-derived mesenchymal stem cells transplanted to the outflow vein immediately after AVF creation could reduce venous stenosis formation by decreasing proinflammatory gene expression in an immunocompetent mouse model (37). In another study, adventitial delivery of allogeneic mouse stem cells obtained from in bred C57BL6/J mice to the adventitia of the stenotic outflow vein after angioplasty was shown to reduce proinflammatory genes

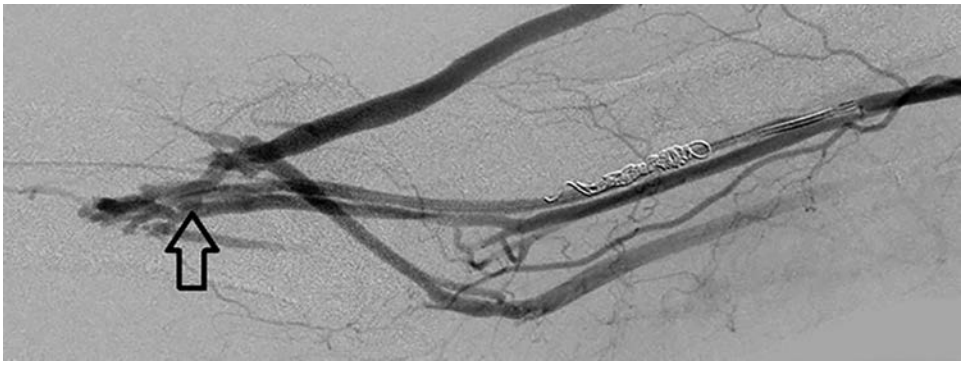

Figure 3. | **Endovascular arteriovenous fistula created with the WavelinQ 4F EndoAVF System.** The arrow denotes the anastomosis. The deep vein is coil-embolized fistula maturation. Image courtesy of Dr. Dheeraj Rajan, MD.

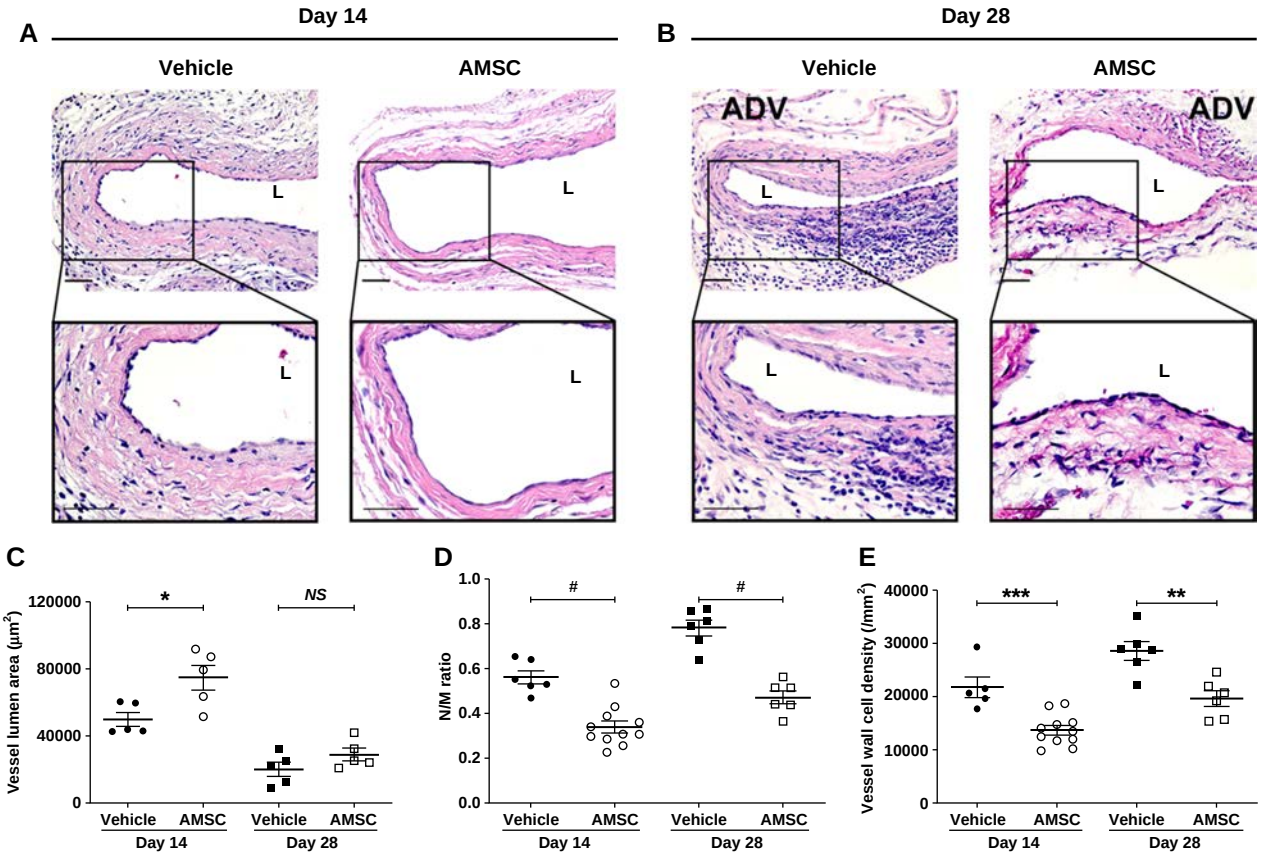

Figure 4. | **AVF stem cell therapy.** Adipose-derived mesenchymal stem cell (ASMC)-treated vessels show outward remodeling compared with controls (A) and (B). Representative hematoxylin and eosin (H&E)–stained sections for vehicle AMSC-treated outflow veins at 14 and 28 days after percutaneous transluminal angioplasty. (C) There was a significant increase in the average lumen area of AMSC-treated vessels compared with controls at day 14 ($P<0.05$). (D) and (E) There was a significant reduction in the average neointima area/media area ratio and vessel wall cell density in the AMSC treated vessels compared with controls at 14 and 28 days after PTA. Scale bar is 50μm. Each scatter plot bar graph represents the mean±SEM of 5–11 animals. Student t test was performed. Significant differences are indicated *$P<0.05$, **$P<0.01$, ***$P<0.001$, $^{\#}P<0.0001$. Adapted from reference 38 with permission. ADV, adventitia: L, lumen.

including IL-1β and TNF-α along with reduction of macrophages, smooth muscle cells, and fibroblasts in the vessel wall. As a result, there was a reduction of tissue fibrosis, improved vascular remodeling, and improved fistula patency (Figure 4) (38). Presently, a clinical trial in patients with AVFs is underway to test the safety and efficacy of autologous stem-cell transplantation for preventing AVF failure (ClinicalTrials.gov: NCT02808208).

Periadventitial Drug Therapy

The adventitial vasa vasorum plays an important role in inflammatory cell migration to the intima, leading to neointimal hyperplasia (39). Although endovascular drug delivery via DCBs and drug-eluting stents is minimally invasive and widely used, one disadvantage of this approach is that the amount of drug delivered to the vessel wall is quite low, due to an increase in blood flow. Direct drug delivery to the adventitia allows for an increased amount of drug to be delivered, and thus may decrease intimal hyperplasia by disrupting the cellular mechanisms involved in venous stenosis formation (40,41).

The biologically active form of vitamin D3 involved in calcium absorption and deposition is 1α,25-dihydroxyvitamin D3 (1α,25$(OH)_2$D3). This chemical also plays an important role in immune responsiveness and cellular differential and proliferation (42), and 1α,25$(OH)_2$D3 has been shown to reduce inflammation (43–45). Studies on periadventitial drug delivery have been mainly preclinical using animal models. A recent study performed in a pig AVF model with CKD showed that adventitial delivery of poly(lactic-co-glycolic acid) nanoparticles encapsulated with 1α,25$(OH)_2$D3, compared with vehicle controls, delivered to the adventitia of the outflow vein after AVF creation reduced venous stenosis formation (Figure 5) by decreasing inflammation and fibrosis (46). Another study using a mouse model showed that poly(lactic-co-glycolic acid) nanoparticles encapsulated with 1α,25$(OH)_2$D3 and delivered to the adventitia of the outflow vein after angioplasty decreased venous neointimal hyperplasia and restenosis by decreasing inflammation and apoptosis pathways (47). Other studies have demonstrated that using microparticles coated with simvastatin to the adventitia of the outflow vein of experimental animals can reduce venous stenosis formation (48). Thus, the application of adventitial delivery of drugs to the arteries and veins at the time of AVF creation may decrease neointimal hyperplasia, thereby improving fistula

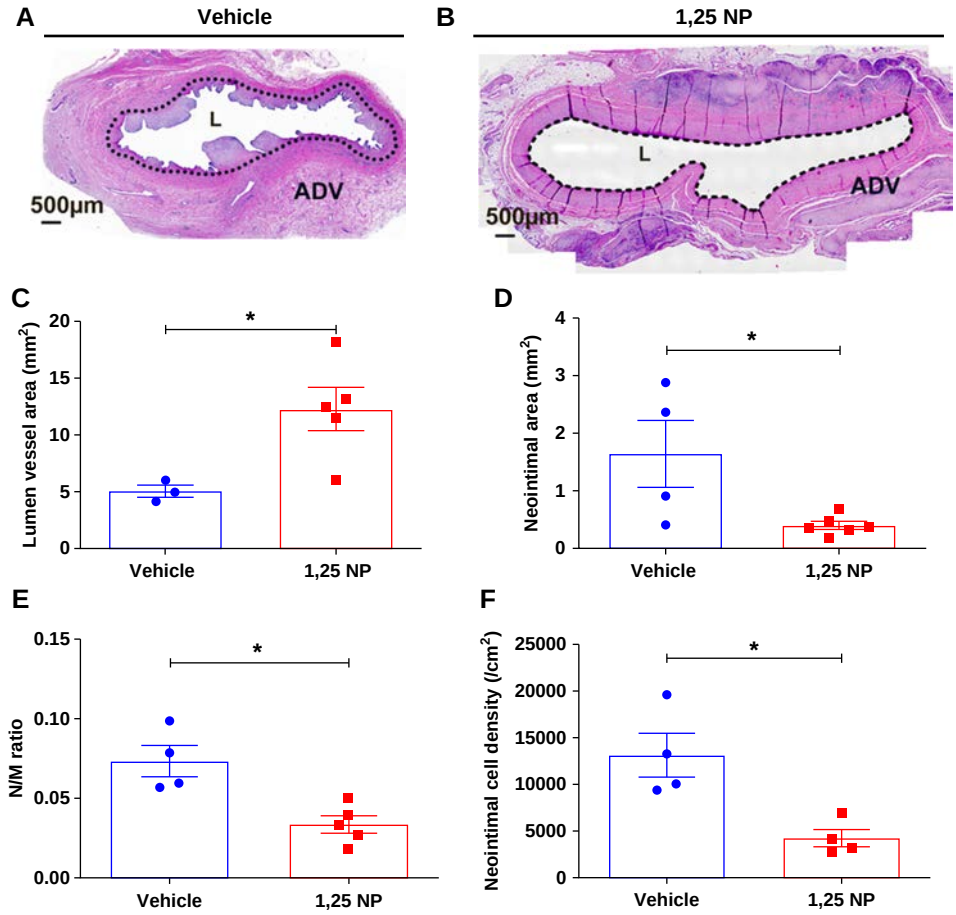

Figure 5. | **Periadventitial drug delivery with vitamin D3.** (A and B) H&E staining of outflow vein treated with poly(lactic-co-glycolic acid) nanoparticles encapsulated with 1α,25(OH)2D3 (1,25 NP) and vehicle groups at day 28 after AVF creation. The neointima and media is identified with a dotted line in the 20x magnification images. Neointima is significantly decreased in the 1,25 NP group compared with vehicle group. (C) The vessel lumen area in 1,25 NP group is significantly increased compared with vehicle group at day 28. (D) The neointima area in 1,25 NP group is significantly decreased compared with vehicle group at day 28. (E) The ratio of neointima/media is decreased in 1,25 NP group compared with vehicle group at day 28. (F) Cell density in the neointima is decreased in 1,25 NP group compared with vehicle group at day 28. Each bar represents mean±SEM of $n \geq 4$. Nonparametric Mann–Whitney test was performed. *$P < 0.05$. Scale bar is 500μm. Adapted from reference 46 with permission.

maturation and proactively decreasing the risk for interventions to sustain patency. Human clinical trials are necessary to determine the clinical efficacy of this drug delivery approach.

Despite the multitude of recent advancements in hemodialysis access, further improvements are still necessary. Whether the panacea for sustaining long-term hemodialysis access is through new AVF creation techniques, better graft designs, stem-cell therapy, innovations in drug delivery, a combination of some, or none at all, remains to be seen. Nevertheless, the current shortcomings create exciting opportunities for research and innovation to optimize hemodialysis access for our patients.

Disclosures

All authors have nothing to disclose.

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Author Contributions

S. Kilari and E. Takahashi wrote the original draft; S. Kilari and S. Misra conceptualized the study; S. Misra was responsible for the funding acquisition, provided supervision, and reviewed and edited the manuscript.

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