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Research Article

RECENT PROGRESS IN DRUG-LOADED ELECTROSPUN NANOFIBERS FOR URETHRAL TISSUE ENGINEERING

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Abstract

Urethral stricture remains a persistent clinical challenge due to inflammation-driven fibrosis, limited vascularization, and inadequate epithelial regeneration following injury. Conventional procedures including dilation, urethrotomy, and graft urethroplasty often fail to provide durable outcomes, with recurrence rates remaining high. Electrospun nanofibers have recently emerged as promising scaffolds capable of mimicking extracellular matrix structure, supporting cellular regeneration, and delivering therapeutic molecules directly to the site of injury. Drug-loaded nanofibers incorporating antibiotics, anti-inflammatory agents, angiogenic factors, and vasodilators such as papaverine have demonstrated improved epithelialization, increased vascularity, and reduced fibrosis in preclinical models. This review summarizes current advances in drug-functionalized electrospun nanofibers for urethral tissue engineering and highlights their potential for translation into future clinical practice.

Keywords: Urethral stricture, Tissue engineering, Electro spinning, Nanofibers, PHBV, Gelatin, Drug delivery, Papaverine, Biofunctional scaffolds.

INTRODUCTION

Urethral stricture disease remains a challenging condition in urologic practice and is characterized by fibrosis and narrowing of the urethral lumen. The disorder commonly develops after trauma, instrumentation, prolonged catheterization, or infection, and once fibrosis begins, it often progresses despite routine clinical interventions. The pathological process is driven by chronic inflammation, impaired vascularity, and excessive extracellular matrix deposition within the corpus spongiosum, resulting in persistent obstruction and recurrent symptoms [1]. Although endoscopic approaches such as dilation and direct vision urethrotomy are widely used, their therapeutic benefit is limited. Recurrence rates frequently exceed 50–70%, reflecting the inability of these procedures to modify the underlying biology of stricture formation [2]. Even urethroplasty considered the most durable option can fail when tissue integration is poor or when local ischemia hinders proper healing. These limitations have intensified interest in regenerative strategies aimed at restoring the structural and functional integrity of the urethra. Effective healing requires coordinated re-epithelialization, organized smooth muscle regeneration, and sufficient angiogenesis, coupled with controlled inflammation and minimal scar formation. However, conventional grafts and synthetic materials lack the microstructural cues and biological activity needed to support this complex process. Electrospun nanofiber scaffolds have emerged as a promising alternative. Their nanoscale architecture resembles the natural extracellular matrix, creating a favorable microenvironment for cell adhesion, migration, and maturation [3]. Beyond structural support, electrospun fibers can be engineered to deliver therapeutic agents such as antibiotics, anti-inflammatory drugs, angiogenic factors, or vasodilators like papaverine directly to the injury site. This localized delivery can modulate the wound environment, reduce fibrosis, and promote vascularized tissue regeneration [4].

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Together, these features position drug-loaded electrospun nanofibers as a compelling platform for next-generation urethral tissue engineering.

Electrospun nanofibers in urethral tissue engineering

Electrospinning has become one of the most widely used techniques for fabricating scaffolds in regenerative urology because it produces nanofibers with diameters and surface properties similar to the natural extracellular matrix (ECM). The resulting fibrous architecture provides high porosity, interconnected pores, and a large surface area features that collectively support cell adhesion, nutrient diffusion, and vascular in growth [5]. These characteristics are particularly relevant to urethral reconstruction, where successful healing requires restoration of a multilayered structure composed of urothelium, smooth muscle, and spongiosal vascular tissue.

Polymer systems used in urethral nanofiber scaffolds

A range of polymers has been employed to generate nanofibrous scaffolds for urethral repair:

- Synthetic polymers such as polycaprolactone (PCL), polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), and polyhydroxyalkanoates (particularly PHBV) provide mechanical strength and controlled biodegradation.
- Natural polymers, including gelatin, collagen, chitosan, and silk fibroin, enhance hydrophilicity and support urothelial and stromal cell attachment.

Blended scaffolds, such as PCL/collagen or PHBV/gelatin, combine the structural stability of synthetic polymers with the biological functionality of natural macromolecules. Studies consistently show that composite nanofibers promote more rapid epithelialization and better integration with host tissue than single-polymer scaffolds [6].

Biological Performance in Preclinical Models

Electrospun scaffolds have shown promising outcomes in animal models of urethral injury. These nanofibers support:

- Rapid urothelial coverage,
- Organized smooth muscle regeneration,
- Increased angiogenesis,
- Reduced inflammation and fibrosis,
- Maintenance of urethral patency.

PHBV-based scaffolds are particularly effective due to their slow degradation and non-acidic byproducts, which help preserve a stable healing environment [7]. Additionally, nanofiber orientation influences tissue outcomes: aligned fibers guide smooth muscle arrangement, while randomly oriented fibers encourage epithelial spreading.

Advantages over conventional grafts

Compared with skin or buccal mucosa grafts, electrospun nanofibers offer several advantages:

- Absence of donor-site morbidity,
- Customizable mechanical and degradation properties,
- Ability to incorporate therapeutic agents,
- Reduced infection risk when functionalized appropriately,
- Biomimetic architecture that promotes natural tissue regeneration.

These features highlight the potential of nanofiber-based scaffolds as next-generation materials for urethral reconstruction.

DRUG-LOADED AND BIOFUNCTIONALIZED NANOFIBERS

A key advantage of electrospun nanofibers in urethral tissue engineering is their capacity to act not only as structural scaffolds but also as local drug-delivery platforms. By incorporating therapeutic agents into the fiber matrix, nanofibers can modulate the biological environment of the urethral wound, addressing the major contributors to stricture formation: **infection, inflammation, ischemia, and fibrosis**. Drug loading can be achieved through blending, surface immobilization, or core–shell electrospinning, enabling precise control over release kinetics [8].

Antibacterial Nanofibers

Bacterial colonization and biofilm formation significantly increase the risk of stricture recurrence. To address this, electrospun scaffolds have been functionalized with:

- Antibiotics (ciprofloxacin, gentamicin),
- Silver nanoparticles,
- Chitosan,
- Zinc oxide nanoparticles.

These antimicrobial modifications reduce bacterial adhesion, inhibit biofilm formation, and help maintain a sterile healing environment. In preclinical urethral models, antibiotic-loaded nanofibers markedly decreased infection-related complications and improved epithelial regeneration compared with unmodified scaffolds [9].

Anti-Inflammatory and Anti-Fibrotic Nanofibers

Persistent inflammation and excessive fibroblast activation contribute to scar formation and stricture recurrence. To counteract this, nanofibers have been engineered to release:

- Corticosteroids,
- Curcumin,
- Losartan,
- Decorin,
- siRNA targeting TGF-β1 or collagen-producing pathways.

These bioactive fibers downregulate pro-fibrotic signaling, reduce collagen deposition, and promote more organized stromal regeneration. Animal studies demonstrate significantly less spongiofibrosis and improved lumen patency when anti-fibrotic agents are delivered via nanofibers [10].

Angiogenic and Vasodilator-Enhanced Nanofibers

Adequate perfusion is essential for urethral repair. Ischemia impairs epithelial and smooth muscle regeneration and accelerates fibrosis. To address this, nanofibers have been functionalized with:

- VEGF,
- FGF2,
- nitric oxide donors,
- papaverine.

Papaverine is particularly attractive because it acts as a vasodilator, phosphodiesterase inhibitor, and smooth muscle relaxant, improving microvascular perfusion and reducing ischemic fibrosis. Papaverine-loaded PHBV/gelatin nanofibers have shown enhanced angiogenesis, improved endothelial cell infiltration, and reduced pro-inflammatory cytokine expression in urethral injury models [11].

Advantages of Drug-Loaded Nanofibers

Drug-functionalized nanofibers provide several benefits compared with systemic therapy:

- High local concentration with minimal systemic toxicity,
- Sustained release for days to weeks,
- Targeted modulation of inflammation and fibrosis,
- Synergistic structural + biological support,
- Reduced recurrence risk through improved wound healing.

These characteristics position drug-loaded nanofibers as a promising adjunct or alternative to traditional graft materials.

PHBV/GELATIN NANOFIBERS

Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) is among the most promising biodegradable polymers for urethral tissue engineering due to its mechanical strength, slow and stable degradation profile, and non-acidic degradation products. However, pure PHBV is relatively hydrophobic and lacks the biological cues necessary for optimal cell adhesion. To address these limitations, PHBV is frequently blended with natural polymers particularly **gelatin**, a denatured collagen derivative rich in bioactive motifs that support cell attachment and proliferation [12].

Advantages of PHBV/Gelatin Blended Nanofibers

The combination of PHBV and gelatin creates a composite scaffold with improved physical and biological characteristics:

- **Enhanced hydrophilicity:** Gelatin introduces polar groups that increase surface wettability, facilitating cell adhesion.
- **Improved mechanical compliance:** PHBV provides durability, while gelatin imparts flexibility closer to native urethral tissue.
- **Balanced degradation:** Blending accelerates PHBV's slow degradation, allowing better synchronization with tissue remodeling.
- **Superior cytocompatibility:** Studies show improved adhesion and proliferation of urothelial and smooth muscle cells on PHBV/gelatin fibers compared with pure PHBV scaffolds [13].

Biological Performance in Urethral Models

In vivo studies demonstrate that PHBV/gelatin nanofibers support several aspects of urethral healing:

- **Rapid epithelialization:** The gelatin component promotes early urothelial coverage.
- **Organized smooth muscle regeneration:** The nanofiber structure guides stromal tissue alignment.
- **Increased angiogenesis:** Improved hydrophilicity supports endothelial cell migration and microvessel formation.
- **Reduced inflammatory response:** Compared with synthetic-only scaffolds, PHBV/gelatin constructs elicit milder foreign-body reactions [14].

These combined effects lead to improved urethral patency and decreased fibrosis in preclinical studies.

Drug-Loaded PHBV/Gelatin Nanofibers

PHBV/gelatin fibers are also excellent carriers for therapeutic agents. Their hybrid composition allows uniform incorporation and sustained release of: antibiotics, anti-inflammatory drugs, growth factors, vasodilators such as papaverine. Papaverine-loaded PHBV/gelatin scaffolds show enhanced microvascular perfusion, reduced macrophage infiltration, and more organized tissue remodeling in urethral defect models [15]. This dual structural–therapeutic approach makes PHBV/gelatin a highly versatile platform for urethral regeneration.

DISCUSSION

The growing body of preclinical evidence demonstrates that drug-loaded electrospun nanofibers offer substantial advantages over conventional grafts for urethral reconstruction. Their ability to mimic extracellular matrix (ECM) architecture enhances cellular attachment, supports urothelial stratification, and promotes organized smooth muscle regeneration features that are rarely achieved with traditional synthetic or autologous materials [16]. These structural benefits align with the broader literature on ECM-mimetic scaffolds, which consistently show improved regenerative outcomes across multiple tissue types [17]. Drug incorporation significantly strengthens the therapeutic potential of nanofiber scaffolds. Antibacterial agents delivered through electrospun fibers effectively reduce bacterial adhesion and biofilm formation, a common cause of stricture recurrence after urethral interventions [18]. Similarly, anti-inflammatory and anti-fibrotic agents, such as corticosteroids, curcumin, or TGF-β1–targeting siRNA, help regulate the dysregulated wound-healing response underlying spongiofibrosis [19]. These findings support the concept that modifying the local immune environment is essential for durable urethral patency. Among the various therapeutic molecules investigated, papaverine has shown particularly promising results. As a phosphodiesterase inhibitor and vasodilator, papaverine improves microvascular perfusion, reduces ischemia-driven fibroblast activation, and promotes endothelial ingrowth mechanisms that directly counteract the pathophysiology of stricture formation [20]. Studies using papaverine-loaded PHBV/gelatin nanofibers report enhanced angiogenesis, reduced inflammatory cytokine expression, and more organized tissue remodeling compared with unloaded scaffolds [21]. These outcomes emphasize the importance of combining structural support with targeted pharmacologic modulation. The PHBV/gelatin composite system appears especially well-suited for urethral tissue engineering. PHBV provides mechanical stability and slow degradation, while gelatin enhances hydrophilicity and cellular affinity. Preclinical models consistently demonstrate improved epithelialization, increased vascular density, and reduced fibrosis when PHBV/gelatin blends are used instead of single-polymer scaffolds [22]. This synergy supports the ongoing shift toward hybrid biomaterials that integrate both synthetic and natural components.

However, despite encouraging data, several limitations must be acknowledged. Most findings derive from rodent or rabbit models, which differ from human urethral anatomy and mechanical stresses. Long-term follow-up data are also limited, particularly regarding chronic inflammatory responses and polymer degradation products. Furthermore, large-scale manufacturing of drug-loaded nanofibers requires stringent quality control to ensure reproducibility in fiber diameter, porosity, and drug-release kinetics all of which significantly influence biological performance. In summary, current evidence supports the use of drug-functionalized electrospun nanofibers as a promising platform for urethral regeneration. Their combined structural and therapeutic functions address major weaknesses of existing surgical treatments. With further refinement and rigorous clinical evaluation, these scaffolds have the potential to become a next-generation solution for urethral stricture disease.

Conclusion

Electrospun nanofibers represent a significant advancement in urethral tissue engineering, offering a biomimetic architecture capable of supporting urothelial, stromal, and vascular regeneration. Among available formulations, PHBV/gelatin composite nanofibers stand out for their balanced mechanical properties, enhanced biocompatibility, and ability to incorporate therapeutic agents. Drug-loaded nanofibers particularly those delivering antibiotics, anti-inflammatory molecules, angiogenic factors, or vasodilators such as papaverine provide targeted modulation of the urethral wound environment, addressing infection, inflammation, ischemia, and fibrosis. Preclinical evidence consistently demonstrates improved epithelialization, reduced collagen deposition, superior vascularization, and better lumen patency with these biofunctional scaffolds. While early findings are promising, translation into clinical practice will require standardized fabrication protocols, detailed long-term safety studies, and controlled clinical trials. Nevertheless, drug-functionalized electrospun nanofibers offer a compelling pathway toward

more effective, biologically driven treatments for urethral stricture disease.

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