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Mini Review

Peptide-Based Therapeutics for Incontinence: Targeting Mitochondrial Organelle Peptides and Nano-Organo Peptides

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Abstract

Background: Pelvic floor disorders (PFDs) represent a significant health burden across sexes. In women, stress urinary incontinence (SUI) and pelvic organ prolapse (POP) affect up to 50% of older adults, with nearly 20% undergoing reconstructive pelvic surgery by age 80. In men, urinary incontinence most commonly arises after prostate surgery, pelvic trauma, or neurogenic injury, with reported prevalence of 10-20% in older populations. Current therapies, including pharmacologic agents, mid-urethral slings, bulking agents, or artificial urinary sphincters, are palliative, associated with complications, and often fail to restore normal sphincter function.

Objective: To evaluate the therapeutic potential of mitochondrial organelle peptides (MOPs) and nano-organo peptides (NOPs) in male and female incontinence, focusing on mechanisms of mitochondrial restoration, oxidative stress reduction, and targeted delivery to pelvic tissues.

Methods: This review synthesizes recent preclinical and translational studies of mitochondrial peptides as well as advances in nanocarrier-based peptide formulations. Mechanistic pathways, clinical applications, and translational challenges are discussed in the context of male and female urinary incontinence.

Results: MOPs stabilize mitochondrial membranes, improve oxidative phosphorylation, and reduce reactive oxygen species, with potential relevance for bladder detrusor, urethral sphincter, and pelvic floor muscle function in both sexes. NOPs enhance peptide stability, enable sustained and localized release, and allow targeted application to pelvic tissues. Early studies suggest synergistic benefits when peptides are combined with mesenchymal stem cell approaches for sphincter regeneration.

Conclusions: MOP and NOP delivery systems represent a novel regenerative strategy for urinary incontinence in both men and women. By directly addressing cellular dysfunction underlying sphincter and pelvic floor weakness, these therapies may shift management from symptomatic compensation toward true tissue restoration. Future clinical trials are essential to evaluate safety, efficacy, and long-term outcomes.

Keywords: Stress Urinary Incontinence, Male Incontinence, Post-Prostatectomy Incontinence, Pelvic Floor Disorders, Mitochondrial Peptides, Nano-Organo Peptides, Regenerative Medicine

Introduction

Urinary incontinence is a common, multifactorial condition that affects both women and men, with profound impacts on quality of life, psychosocial health, and healthcare costs. In women, pelvic floor disorders (PFDs) are especially prevalent, with stress urinary incontinence (SUI) and pelvic organ prolapse (POP) affecting 30-50% of older adults [1]. By the age of 80, nearly 20% of women will have undergone reconstructive pelvic surgery for one of these conditions, and approximately 30% will require reoperation [2]. SUI, characterized by involuntary urine leakage during exertion, frequently results from childbirth-associated urethral sphincter injury and is exacerbated by age-related changes and estrogen deficiency [3]. In men, urinary incontinence most often occurs following prostate surgery, particularly radical prostatectomy, where injury to the sphincteric complex and its innervation can result in post-prostatectomy incontinence (PPI) [4]. Male incontinence may also arise from pelvic trauma, neurologic disease, or aging-related degeneration of urethral sphincter function [5]. Reported prevalence varies but may affect 10-20% of men over 65, with substantial consequences for functional independence and emotional well-being [6].

Current treatment options remain largely mechanical or palliative. In women, mid-urethral sling procedures and bulking agents are widely used, while in men, artificial urinary sphincters or male slings are considered the standard of care [7]. While effective for many, these interventions do not restore native sphincter function, rely on prosthetic or inert substitutes, and carry risks such as erosion, infection, or mechanical failure. Furthermore, regulatory scrutiny surrounding synthetic meshes underscores the uncertainty of long-term safety and durability [8].

Given these limitations, there is an urgent need for regenerative strategies that can restore the structural and functional integrity of the urethral sphincter and pelvic floor across sexes. Mitochondrial organelle peptides (MOPs), target fundamental mechanisms of mitochondrial dysfunction, oxidative stress, and cellular energy decline, while nano-organo peptide delivery systems (NOPs) enable localized, controlled, and sustained peptide administration. Together, these therapies hold promise for shifting incontinence management from symptomatic compensation toward true functional regeneration in both men and women.

Pathophysiology of Incontinence and Role of Mitochondria

Mitochondria play a pivotal role in maintaining cellular homeostasis within bladder smooth muscle, the urethral sphincter, and pelvic floor tissues by regulating energy metabolism, calcium handling, and redox balance [9]. Disruption of mitochondrial function, whether due to aging, childbirth-related trauma, or surgical injury, has been increasingly recognized as a central contributor to pelvic floor dysfunction and incontinence [10]. Deficits in oxidative phosphorylation (OXPHOS) compromise ATP production, undermining the contractile strength and endurance of both detrusor and sphincter cells. Concurrently, excess generation of reactive oxygen species (ROS) accelerates oxidative stress, triggering tissue fibrosis, neuromuscular degeneration, and impaired signaling cascades that further exacerbate dysfunction [11]. In parallel, diminished mitochondrial biogenesis restricts the tissue's ability to repair and adapt, thereby limiting long-term regenerative potential. Taken together, these interrelated mechanisms establish mitochondrial decline as a critical driver of continence failure. Accordingly, interventions designed to restore mitochondrial stability and efficiency represent a rational and potentially transformative therapeutic strategy.

Mitochondrial Organelle Peptides (MOPs)

Among the most studied mitochondrial organelle peptides are SS-31 (Elamipretide) and MOTS-c, each targeting distinct yet complementary aspects of mitochondrial dysfunction. SS-31 is a synthetic aromatic-cationic tetrapeptide that selectively binds to cardiolipin, a phospholipid located in the inner mitochondrial membrane. This interaction stabilizes mitochondrial cristae architecture, preserves electron transport chain integrity, and enhances ATP production while simultaneously reducing ROS generation [12]. Chen et al recently revealed that the incidence of SUI is associated with mitochondrial homeostasis dysregulation following oxidative stress in the fibrous connective tissue of the pelvic floor [13], providing novel insights into the role and associated mechanism of ameliorating oxidative stress-induced mitochondrial as a potential therapeutic target for SUI. In preclinical models of ischemia-reperfusion and muscle fatigue, SS-31 has been shown to restore contractile capacity, attenuate oxidative stress, and improve neuromuscular endurance, effects that are directly translatable to the detrusor and urethral sphincter in the context of continence disorders. Sweetwyne and colleagues demonstrated SS-31 treatment reduced markers of parietal epithelial cell activation and improved cytoskeletal integrity. This was accompanied by higher glomerular endothelial cell density (CD31). Thus, despite initiating therapy in late-age mice, a short course of SS-31 has protective benefits on glomerular mitochondria, accompanied by temporal changes to the glomerular architecture. MOTS-c, by contrast, is a mitochondrial-derived peptide encoded within mitochondrial DNA that exerts systemic metabolic effects. It activates the AMP-activated protein kinase (AMPK) pathway, stimulating mitochondrial biogenesis, improving glucose utilization, and enhancing skeletal and smooth muscle resilience [14] Experimental evidence suggests that MOTS-c may counteract age- and menopause-related declines in muscle strength, offering a therapeutic avenue for stress urinary incontinence in women, while also potentially mitigating post-prostatectomy sphincter weakness in men [15]. Together, these peptides exemplify how targeted modulation of mitochondrial pathways can address the fundamental cellular deficits underlying incontinence, positioning them as leading candidates in the development of regenerative pelvic floor therapies.

Nano-Organo Peptides (NOPs)

While mitochondrial peptides such as SS-31 and MOTS-c pro-

vide direct bioenergetic and cytoprotective benefits, their therapeutic potential is constrained by rapid degradation, limited systemic half-life, and suboptimal tissue penetration. NOP delivery systems have emerged as a solution to these barriers, enabling controlled, sustained, and targeted administration to pelvic floor and lower urinary tract tissues [16]. By encapsulating peptides within liposomes, polymeric nanoparticles, or nanogels, NOP platforms protect against enzymatic degradation, prolong circulation time, and enhance tissue-specific uptake. Moreover, nanotechnology-based drug delivery platforms are being increasingly explored for their capacity to selectively target the reproductive system, thereby enhancing treatment effectiveness while minimizing adverse effects. Recent work has emphasized the structural and functional features of the female upper genital tract, particularly the role of mucosal barriers in shaping both systemic and localized drug distribution. Progress in nano-formulated therapeutics demonstrates improved biocompatibility, prolonged therapeutic activity, and controlled release, underscoring their promise as innovative strategies for the management of disorders affecting the female reproductive tract [17]. For continence applications, intravesical or periurethral delivery of peptide-loaded nanocarriers offers the ability to localize therapy directly to the bladder detrusor or urethral sphincter, minimizing systemic exposure and associated side effects [18]. Moreover, stimuli-responsive nanocarriers can be engineered to release their peptide payload in response to pH, enzymatic activity, or oxidative stress, providing precision dosing in diseased microenvironments. Preclinical studies in bladder and muscle models have demonstrated that nanoparticle-conjugated peptides achieve greater tissue penetration and functional recovery than free peptide administration [19]. These findings underscore the potential of NOPs to not only improve pharmacokinetics and bioavailability, but also to enable regenerative interventions that are spatially and temporally tailored to the pathophysiology of incontinence.

Results and Discussion

Mitochondrial dysfunction is increasingly recognized as a central driver of pelvic floor decline and incontinence. In bladder smooth muscle, the urethral sphincter, and pelvic floor tissues, mitochondria regulate energy metabolism, calcium signaling, and redox balance. With aging, childbirth trauma, or surgical injury, impaired mitochondrial function reduces oxidative phosphorylation efficiency, compromises ATP production, and increases reactive oxygen species (ROS) accumulation. These changes diminish contractile strength, promote tissue fibrosis, and restrict the regenerative capacity of pelvic structures, collectively undermining continence mechanisms [20].

Targeting these deficits with MOPs represents a rational therapeutic strategy. By restoring ATP synthesis and reducing ROS generation, MOP have been shown to preserve muscle contractility and neuromuscular integrity in preclinical models. Complementing this mechanism, MOTS-c, a mitochondrial-derived peptide encoded within mitochondrial DNA, activates AMPK, stimulating mitochondrial biogenesis and enhancing glucose utilization. Through these actions, MOPs support skeletal and smooth muscle resilience, offering particular relevance for age- and menopause-related sphincter decline in women and for sphincter injury following prostatectomy in men. Together, these peptides demonstrate the potential to directly address cellular bioenergetic failure at the core of continence dysfunction.

Despite these benefits, peptide therapeutics face inherent challenges, including rapid degradation, short half-life, and limited tissue penetration. NOP delivery systems address these limitations by encapsulating bioactive peptides within liposomes, nanoparticles, or nanogels. Such carriers shield peptides from enzymatic breakdown, extend circulation time, and enhance uptake into target tissues. Importantly, periurethral or intravesical delivery of peptide-loaded nanocarriers enables localized therapy at sites critical for continence, reducing systemic exposure and side effects. Furthermore, stimuli-responsive nanocarriers, engineered to release their payload in response to pH, enzymatic activity, or oxidative stress, offer the ability to synchronize peptide delivery with disease-specific microenvironmental changes. Early preclinical studies suggest that nanoparticle-conjugated peptides achieve superior tissue penetration and functional recovery compared to free peptide administration.

Taken together, the integration of MOPs with NOP delivery strategies represents a next-generation therapeutic paradigm. By simultaneously restoring mitochondrial bioenergetics and ensuring precise, sustained delivery, these approaches hold promise to move incontinence management beyond symptomatic compensation and toward true regenerative restoration of pelvic floor and sphincter function.

Synergistic Regenerative Strategies

While mitochondrial peptides and nano-organo delivery systems independently address critical aspects of cellular dysfunction in incontinence, their true therapeutic potential may be realized in combination with regenerative approaches such as stem cell therapy and tissue engineering. Mesenchymal stem cells (MSCs), for example, have been investigated for urethral sphincter regeneration and pelvic floor repair, demonstrating the ability to differentiate into smooth muscle or fibroblast-like cells and to secrete trophic factors that support angiogenesis, neuroprotection, and extracellular matrix remodeling [21]. However, the survival and functional integration of transplanted cells are frequently limited by hostile microenvironments characterized by oxidative stress, hypoxia, and mitochondrial instability.

In this context, MOPs offer a complementary strategy by stabilizing mitochondrial membranes, enhancing oxidative phosphorylation, and reducing ROS, thereby creating conditions that favor stem cell engraftment and persistence. Similarly, NOP systems enable precise delivery of bioactive peptides to the periurethral or detrusor tissues, ensuring sustained support of both host and transplanted cells. This dual approach not only improves cellular survival but also enhances functional integration, thereby amplifying regenerative outcomes.

Furthermore, personalized strategies can be envisioned in which biomarkers of mitochondrial function, inflammatory status, or stem cell viability guide the selection and timing of combined therapies. For instance, circulating indicators of oxidative stress or mitochondrial efficiency may help identify patients most likely to benefit from peptide supplementation alongside cell-based interventions. Tissue-engineered scaffolds seeded with MSCs could be further optimized by embedding peptide-loaded nanocarriers, allowing for localized and temporally controlled release of agents directly into the sphincter complex. Collectively, the integration of MOPs, NOPs, and regenerative cell therapies represents a multimodal approach to incontinence management, one that addresses the underlying cellular and structural deficiencies rather than relying solely on mechanical compensation. Such synergistic strategies hold promise to transform treatment paradigms by promoting durable restoration of continence mechanisms across both women and men.

Translational Challenges

Although MOP and NOP delivery platforms hold significant promise for the management of incontinence, several translational hurdles must be addressed before these therapies can move from bench to bedside. A primary challenge is the limited clinical evidence directly linking mitochondrial dysfunction to pelvic floor disorders in humans. While preclinical studies demonstrate improved muscle endurance, metabolic resilience, and neuromuscular function, robust data in bladder, urethral sphincter, or pelvic floor models remain sparse. Establishing disease-specific mechanistic pathways and confirming therapeutic efficacy in clinically relevant models will be critical. A second challenge lies in delivery optimization. Peptide bioavailability and pharmacokinetics are strongly influenced by the route of administration. Systemic delivery risks rapid clearance and off-target effects, whereas local administration may provide higher tissue concentrations but requires procedural expertise and repeated interventions. Balancing therapeutic precision with patient acceptability will be essential for adoption. Safety and long-term tolerability also require careful evaluation. Although MOPs are generally well tolerated in early studies, the chronic administration that would likely be necessary for PFD has not been systematically assessed. Similarly, nanocarrier systems introduce concerns regarding immunogenicity, degradation products, and potential off-target biodistribution. Regulatory agencies will require stringent safety data and reproducibility of nanoparticle synthesis before clinical translation. Another barrier is the heterogeneity of incontinence phenotypes across sexes, ages, and etiologies. Women may present with childbirth-related sphincter injury or menopausal decline, whereas men more commonly experience post-prostatectomy sphincter damage. These differences necessitate tailored therapeutic strategies and may complicate clinical trial design. Furthermore, defining appropriate biomarkers of response will be necessary to stratify patients and monitor therapeutic impact. Finally, regulatory and ethical considerations surrounding advanced biologics and nanotechnologies remain complex. Peptide-based therapies that blur the line between biologic and small-molecule drugs may require hybrid regulatory pathways, while nanoparticle formulations must demonstrate manufacturing reproducibility, stability, and quality control under Good Manufacturing Practice (GMP) standards. These issues will add time and cost to clinical translation but are essential for ensuring safety and efficacy. Taken together, these challenges underscore that while mitochondrial and nanocarrier peptide strategies represent a promising frontier for incontinence therapy, their clinical integration will require a rigorous, multidisciplinary effort spanning basic science, translational research, regulatory science, and clinical trial design.

Conclusion

Urinary incontinence remains a pervasive and debilitating condition in both women and men, with current treatment options limited to mechanical or pharmacologic approaches that often fail to restore native function. The high recurrence rates following surgical interventions, along with regulatory concerns regarding synthetic mesh and other prosthetic devices, highlight the urgent need for therapies that address the root causes of sphincter and pelvic floor dysfunction. MOPs offer a novel means of directly targeting bioenergetic and oxidative stress pathways that underlie muscle weakness, neural injury, and tissue degeneration in continence mechanisms. Parallel advances in NOP delivery systems further expand this therapeutic potential by ensuring stability, prolonging half-life, and enabling localized delivery to the bladder, sphincter, and pelvic floor. Together, these approaches have the capacity to shift the paradigm from symptomatic relief toward regenerative restoration. Future progress will depend on rigorous translational research. Key priorities include developing clinically relevant models of stress urinary incontinence and post-prostatectomy incontinence, identifying biomarkers of mitochondrial function and therapeutic response, and conducting well-designed clinical trials to evaluate safety, efficacy, and long-term durability. Equally important will be the integration of peptide-based strategies with regenerative platforms such as mesenchymal stem cells and tissue-engineered scaffolds, offering a multimodal approach that addresses both cellular dysfunction and structural deficits. By converging mitochondrial biology, nanotechnology, and regenerative medicine, peptide-based therapies hold the potential to transform the treatment of incontinence. If successfully translated into clinical practice, these innovations could move beyond palliative support to achieve lasting functional regeneration, significantly improving quality of life for millions of affected individuals worldwide.

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