



REFRACTORY ERECTILE DYSFUNCTION AND PEYRONIE'S DISEASE: CURRENT PERSPECTIVES ON REGENERATIVE AGENTS AND NEXT-GENERATION DEVICES

Jacobo Giraldo
Henao

MD. Universidad de Manizales

ABSTRACT

Refractory erectile dysfunction and Peyronie's disease frequently present together, resulting in severe anatomical deformities, sexual disability, and psychological distress. While conventional management relies on phosphodiesterase type 5 inhibitors, intracavernosal injections, and mechanical devices, a substantial subset of patients demonstrates treatment resistance. This narrative review synthesizes current evidence regarding novel restorative therapies and advanced prosthetic devices. Regenerative strategies—including low-intensity extracorporeal shockwave therapy, platelet-rich plasma, and stem cell transplantation—target microvascular rarefaction, smooth muscle apoptosis, and tunical fibrosis, although high-level clinical evidence supporting routine use remains limited. Conversely, inflatable penile prosthesis implantation remains the gold standard definitive therapy for coexisting end-stage erectile dysfunction and stable penile curvature, often combined with manual modeling, tunical incision, or grafting.

KEYWORDS : Erectile Dysfunction; Peyronie Disease; Penile Prosthesis; Regenerative Medicine.

INTRODUCTION

Erectile dysfunction and Peyronie's disease represent two distinct yet profoundly intertwined pathological entities that impair male sexual function, physical intimacy, and mental well-being (1). Erectile dysfunction involves the consistent inability to attain or sustain a penile erection sufficient for satisfactory sexual performance, arising from vasculogenic, neurogenic, psychogenic, or structural etiologies (2). In contrast, Peyronie's disease is an acquired connective tissue disorder characterized by localized inflammation, excessive collagen deposition, and inextensible fibrous plaque formation within the tunica albuginea of the penis (3). The epidemiological overlap between both disorders is substantial, with erectile dysfunction diagnosed in up to half of men suffering from Peyronie's disease (1) (3). When structural plaques compromise cavernosal compliance or lead to veno-occlusive dysfunction, conservative pharmacotherapies often fail, precipitating refractory disease states (2).

Traditional management ladders prioritize non-invasive pharmacological modalities, specifically oral phosphodiesterase type 5 inhibitors (1). When first-line oral regimens prove inadequate, clinical pathways recommend second-line alternatives such as vacuum erection devices, intraurethral alprostadil suppositories, or intracavernosal injections comprising vasoactive agents like alprostadil, papaverine, and phentolamine (2) (4). However, patients presenting with extensive microvascular damage, radical pelvic surgery sequelae, severe diabetic neuropathy, or dense tunical calcification frequently become refractory to maximum pharmacotherapy (2). Concurrently, conservative options for active or chronic Peyronie's disease, including oral antioxidants, traction therapy, or intralesional collagenase injections, demonstrate variable success rates, particularly in cases marked by multidirectional curvature, shortening, or severe cavernosal smooth muscle loss (3) (5).

Given these limitations, translational research has pivoted toward two therapeutic frontiers: biological restorative agents aiming to halt or reverse structural cavernosal damage, and advanced prosthetic devices engineered to mechanically reconstitute axial rigidity and anatomical alignment (4) (6). Restorative modalities, such as low-intensity extracorporeal shockwave therapy, platelet-rich plasma formulations, and mesenchymal stem cell transplantation, strive to induce angiogenesis, mitigate oxidative stress, modulate excessive collagen cross-linking, and regenerate dysfunctional neurovascular tissue (4) (7). Meanwhile, contemporary third-generation inflatable penile prostheses, integrated with antimicrobial surface modifications and combined with tailored intraoperative modeling techniques, offer definitive

functional restoration for severe concomitant disease (6) (8). Understanding the evolving synergy between biological modulation and mechanical reconstruction is essential to modern andrological practice (1) (6).

Methods

A comprehensive literature search was conducted across four electronic databases: PubMed, Scopus, Embase, and Web of Science. The retrieval strategy captured investigations examining regenerative therapies, low-intensity shockwaves, platelet-rich plasma, stem cell applications, and penile prosthesis surgery in adult patients diagnosed with refractory erectile dysfunction and Peyronie's disease. Following the primary screening of identified titles and abstracts, 15 studies were selected for full-text evaluation. T

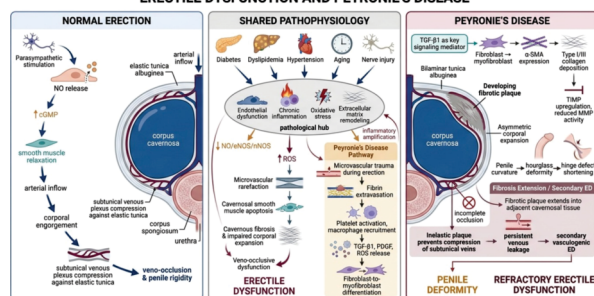
Pathophysiology of Dual Disease

The common denominator linking erectile dysfunction and Peyronie's disease is endothelial dysfunction, structural extracellular matrix remodeling, and chronic inflammatory signaling within the cavernous architecture (1) (3). Healthy erection relies on intact autonomic innervation and parasympathetic nitric oxide release, which drives cyclic guanosine monophosphate accumulation and cavernosal smooth muscle relaxation (2). This relaxation permits arterial inflow, corporal engorgement, and mechanical compression of the subtunical venular plexus against an elastic tunica albuginea, establishing the veno-occlusive mechanism (2) (9). In refractory erectile dysfunction, chronic conditions such as diabetes mellitus, dyslipidemia, arterial hypertension, and cavernous nerve injury induce relentless oxidative stress, microvascular rarefaction, and smooth muscle cell apoptosis, culminating in corporal fibrosis and veno-occlusive incompetence (1) (9).

The development of Peyronie's disease is classically triggered by microvascular trauma to the erect penis during coitus, particularly in genetically susceptible individuals (3). Mechanical shearing stress disrupts the bilaminar tunica albuginea, initiating microvascular extravasation, fibrin deposition, and platelet activation (3) (10). Activated platelets and infiltrating macrophages release high concentrations of transforming growth factor-beta 1, platelet-derived growth factor, and reactive oxygen species (5) (10). Transforming growth factor-beta 1 serves as the central molecular driver of the fibrotic response, inducing the differentiation of resident quiescent fibroblasts into contractile myofibroblasts (5) (10). These myofibroblasts persistently express alpha-smooth muscle actin, generate disorganized type I and III collagen fibrils, and inhibit matrix metalloproteinases via tissue inhibitor of metalloproteinase upregulation (10).

Over time, this unchecked inflammatory state forms an inextensible, dense, and occasionally calcified plaque within the tunica albuginea (3) (5). When the adjacent erectile tissue expands during tumescence, the inelastic fibrous segment restricts corporal elongation, generating classic clinical manifestations: severe angular deviation, hourglass deformities, hinge defects, and marked loss of penile length (3) (8). Crucially, the fibrotic process frequently extends inward into the underlying erectile bodies, destroying the adjacent subtunical cavernous tissue (1) (10). Consequently, corporal veno-occlusive dysfunction develops, as the inelastic plaque prevents proper compression of the emissary veins against the tunica, precipitating secondary vasculogenic erectile failure that is inherently resistant to conventional vasoactive therapy (1) (2).

**PATHOPHYSIOLOGY OF THE DUAL DISEASE:
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Pathophysiological mechanisms linking erectile dysfunction and Peyronie's disease. Schematic representation of the shared vascular, inflammatory, and fibrotic mechanisms underlying both conditions. In erectile dysfunction, endothelial dysfunction, oxidative stress, microvascular rarefaction, smooth muscle apoptosis, and cavernous fibrosis impair nitric oxide–cGMP-mediated smooth muscle relaxation and the veno-occlusive mechanism.

Regenerative Agents: Emerging Restorative Strategies

Restorative therapies represent a conceptual shift from palliative symptomatic treatment toward structural and molecular tissue rejuvenation (4). Among non-invasive restorative techniques, low-intensity extracorporeal shockwave therapy has gained considerable clinical and research attention (4) (11). Low-intensity shockwaves deliver acoustic energy pulses to the corporal tissue, generating mechanical shear stresses that trigger cellular mechanotransduction (11). This biological cascade promotes the expression of vascular endothelial growth factor, endothelial nitric oxide synthase, and proliferating cell nuclear antigen (4) (11). Preclinical and clinical models demonstrate that shockwave protocols can stimulate local neovascularization, promote the recruitment of endogenous circulating progenitor cells, and restore cavernous endothelial architecture (11) (12). In Peyronie's disease, shockwave energy is sometimes applied to alleviate intractable pain during the early active phase; however, randomized clinical trials demonstrate that shockwaves do not degrade established calcified plaques or reliably reduce penile curvature, confining their role to pain control or adjunctive vasculogenic erectile therapy (4) (12).

Platelet-rich plasma represents an autologous biologic alternative prepared through centrifugal concentration of whole blood, yielding supra-physiological concentrations of platelets suspended in a modest volume of plasma (7) (13). When activated at the injection site, platelet alpha-granules degranulate to discharge an abundant cocktail of bioactive factors, including transforming growth factor-beta isoforms, platelet-derived growth factor, vascular endothelial growth factor, basic fibroblast growth factor, and epidermal growth factor (7). In cases of refractory erectile dysfunction, intracavernosal administration of platelet-rich plasma is hypothesized to accelerate microvascular repair, dampen local oxidative stress, and stimulate smooth muscle

regeneration (7) (13). When utilized in Peyronie's disease, investigators postulate that specific growth factor ratios within platelet-rich plasma may attenuate active fibroblastic activity and promote collagen remodeling (7). Nevertheless, clinical evidence supporting platelet-rich plasma remains hindered by substantial protocol heterogeneity, including variable centrifugation parameters, inconsistent platelet concentration thresholds, lack of standardization regarding leukocyte inclusion, and a paucity of long-term placebo-controlled trials (7) (13).

Stem cell therapy stands at the technological forefront of cellular regenerative medicine (4) (14). Mesenchymal stem cells derived from bone marrow, adipose tissue, or umbilical cord tissue possess multipotent differentiation capacity and remarkable immunomodulatory properties (14). Although initial theories suggested that implanted stem cells directly differentiated into endothelial cells and cavernous smooth muscle, robust contemporary investigations confirm that their primary mechanism of action is mediated through paracrine and secretome signaling (4) (14). Mesenchymal stem cells secrete extracellular vesicles and exosomes rich in neurotrophic factors, such as brain-derived neurotrophic factor, nerve growth factor, and angiopoietin-1, which downregulate systemic inflammation, halt cavernosal apoptosis, and facilitate cavernous nerve regeneration following radical prostatectomy or pelvic neural injury (14). In animal models of Peyronie's disease, local stem cell administration during the acute inflammatory phase suppresses myofibroblast differentiation and halts plaque maturation by downregulating transforming growth factor-beta 1 signaling (4). Despite these promising experimental findings, regulatory hurdles, cell survival constraints, potential tumorigenicity, high production costs, and heterogeneous clinical translation keep stem cell applications largely confined to investigational protocols and controlled clinical trials (4) (14).

Next-Generation Devices and Surgical Paradigms

For individuals with end-stage refractory erectile dysfunction accompanied by mature, stable Peyronie's disease deformities, penile prosthesis implantation remains the definitive, standard-of-care therapeutic intervention (6) (8). Modern prosthetic options encompass malleable semi-rigid rods and three-piece inflatable penile prostheses (6). Semi-rigid devices provide constant rigidity with manual positioning simplicity, making them suitable for individuals with compromised manual dexterity or financial limitations (6). However, the three-piece inflatable penile prosthesis—comprising paired intracavernosal cylinders, a scrotal control pump, and a fluid-filled reservoir placed in the preperitoneal space or space of Retzius—provides superior rigidity, natural detumescence, and markedly superior patient and partner satisfaction rates exceeding 90% (6) (8).

Technological enhancements in prosthesis manufacturing have decreased mechanical failure rates and surgical complications (6) (15). Next-generation inflatable devices incorporate advanced polymer formulations, expanded girth and length expansion capabilities, and low-profile pumps equipped with tactile lockout valves to prevent auto-inflation (6). Crucially, modern devices integrate specialized hydrophilic coatings or factory-impregnated antibiotic combinations—such as rifampin and minocycline—that inhibit bacterial biofilm formation and dramatically diminish postoperative prosthetic infection rates from historical levels of 5% down to under 1% in primary implantations (6) (15).

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