Mini-Review

DOI: 10.5582/irdr.2019.01130

Advances in stem cell therapy for the treatment of Peyronie's disease

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SUMMARY Peyronie's disease (PD) is a connective tissue disorder of the penis characterized by fibrosis and plaque formation within the tunica albuginea. PD is characterized by painful penile curvature that impairs sexual intercourse. Stem cell therapy is one of the recent non-invasive treatment options for patients with PD and it has promising results. Stem cells are undifferentiated cells that are capable of self-renewal and differentiation, promoting the repair of tissues via their immunomodulatory and anti-inflammatory action. Adipose-derived stem cells (ADSC) are used most widely due to their abundant tissue source and ease of isolation. Multiple studies have indicated the efficacy of stem cell therapy as a potential treatment for fibrotic diseases. Clearly, ADSCs may represent a way to treat and prevent PD in both rat and human models. Further clinical studies are needed to confirm the efficacy of stem cell therapy for PD in humans.

Keywords Peyronie's disease, stem cell, adipose stem cells, fibrosis, regeneration

1. Introduction

Peyronie's disease (PD) is an uncommon condition involving middle-aged men. It is caused by an inflammation in the tunica followed by scarring and penile curvature. It is considered to be a fibrotic disorder of the penis that is characterized by the formation of collagen plaques on the tunica albuginea that may cause penile curvature, narrowing, and shortening that subsequently lead to erectile dysfunction (ED) (*1,2*). The prevalence of PD varies because it is usually underreported by men. Schwarzer *et al*. conducted a large survey involving 8,000 men and noted a prevalence of 3.2% (*3*). DiBenedetti *et al*. reported a prevalence of 13% among males ages 18 years and older; this figure includes men diagnosed with, treated for, or who recently reported penile symptoms of PD (*4*).

Patients with PD present early after the onset of the disease (within 6 months) with penile pain and curvature upon erection. PD is characterized by a palpable plaque in the tunica albuginea and is usually associated with ED. It occurs in middle-aged men, most of whom are between 40 and 59 years. Penile curvature is the first symptom of the disease and develops in 94% of patients (*5*). ED is usually present in patients with PD, developing in 30-50% of those patients (*6,7*). Multiple causes can contribute to ED due to PD such as arterial insufficiency, venous insufficiency, a psychologic effect, or geometric variation (*8-11*).

One of the theories helping to explain the pathophysiology of PD is microvascular trauma. This results in edema, inflammation, and fibrin deposition within the tunica albuginea. During the acute phase of PD, transforming growth factor (TGF)-β1 is overexpressed, and this induces fibroblasts to increase collagen synthesis (*12,13*). TGF-β1 can induce its own synthesis and contributes to continuous fibrotic changes (*14*). An autoimmune theory of the pathophysiology of PD was proposed since the serology of patients with PD has detected high titers of anti-elastin antibodies (*15*). PD is associated with Dupuytren's contracture and certain human leukocyte antigen subtypes (*16,17*). Multiple genes such as matrix metalloproteinases (MMP2, MMP9) and osteoblast-specific factor 1 are overexpressed in PD and Dupuytren's contracture (*18,19*).

PD is clinically diagnosed based on a detailed history and a penile examination. Measurement of penile curvature and palpation of plaque are important elements of this examination (*19*). There are 2 phases of PD, acute and chronic. During the acute phase or inflammatory phase, there is penile pain in a flaccid or erect state and palpable plaque; this phase typically

lasts for 12-18 months after onset; this is followed by the chronic phase where pain disappears and penile curvature stabilizes (*20*).

In general, medical treatment is often used during the acute phase of the disease whereas surgery is used during the stable phase (*21*). Non-surgical treatment includes oral or intralesional pharmacotherapy. Oral therapies include vitamin E and paraaminobenzoate, colchicine, tamoxifen, and acetyl-L-carnitine. Intralesional injection therapy includes injection with interferon-alpha-2b, verapamil, or collagenase. Surgery is reserved for patients who do not respond to medical therapy or for men with severe penile curvature that affects sexual intercourse after stabilization of the disease (*21-23*). Surgical procedures are either penile shortening or penile lengthening to correct curvature; the procedure depends on penile length and the degree of curvature (*24*).

Regenerative medicine represents a novel therapy for the treatment of PD using mesenchymal stem cell therapy with both curative and preventive potential. Stem cells are self-renewing cells with a high degree of plasticity that can differentiate into multiple cell lines; they can be used to repair genetically damaged tissue or altered organs (*25*). Stem cells can be derived from embryonic, fetal, and adult tissue. They can be used in tissue engineering to repair a disrupted process (*26*). Many studies have described the use of stem cells to treat urologic conditions such as PD, incontinence, infertility, and ED (*27*).

2. Rationality behind using stem cell therapy to treat PD

Mesenchymal stem cells (MSCs) have immunomodulatory roles. Adipose-derived stem cell (ADSC) are easy to isolate and lack major histocompatibility complex-II expression, and their immunosuppressive action is mediated by prostaglandin E2 (*28*). The mechanism of ADSC therapy is not well known. After their differentiation, they can secrete growth factors promoting angiogenesis. They can act also by modulating the immune response via secretion of galectin-1 and -3, which are essential in T-cell suppression, resulting in downregulation of the inflammatory response. Thus, they promote wound repair and regeneration (*29,30*). In addition, ADSC decrease fibrosis by down-regulating profibrogenic molecules such as COL1A1 and ACTA2, thus regressing the fibrotic process in many diseases such as chronic renal fibrosis (*31*) and lung fibrosis (*32*).

Multipotent stromal cells have demonstrated efficacy in the treatment of ED due to cavernous nerve injury in multiple animal models via cell differentiation and local paracrine action (*33*). In addition, ADSCs injected into the penis of impotent type 2 diabetic rats can improve erectile function through their paracrine effect (*34*).

3. Studies corroborating the use of stem cell therapy to treat PD

In 2013, the first study used ADSCs to treat PD in an animal model; TGF-β1 was used to induce fibrosis within the tunica albuginea of rats. One day after injection of TGF-β1, human ADSCs were administered in a xenogeneic manner. Erectile function significantly improved after ADSC treatment (*35*). This is the first study to use xenogeneic cells that were transplanted into immunocompetent animals without the use of immunosuppressants, and the results were promising. ADSCs are known to have both immunomodulatory

Table1. Animal and human clinical studies corroborating the role of stem cell therapy in the treatment of PD

Study	Year	Stem cells	Studies were undertaken in humans or animals	Outcomes
Levy JA *et al*. (*39*)	2015	Placental matrix-derived mesenchymal stem cells	Humans	Peak systolic velocity and penile curvature improved significantly 6 weeks, 3 months, and 6 months after treatment. Seven of 10 fibrotic plaques in the tunica albuginea disappeared completely at 3 months.
Castiglione *et al*. (*35*)	2013	Human adipose-derived stem cells	Animals	Erectile function improved during the acute phase of PD.
Gokce *et al*. (*37*)	2014	Rat adipose-derived stem cells	Animals	Erectile function improved during the acute and chronic phase of PD.
Gokce *et al*. (*38*)	2015	Genetically modified adipose tissue-derived stem cells with human interferon α-2b	Animals	Erectile function improved during the acute and chronic phase of PD.
Castiglione *et al*. (*36*)	2019	Human adipose-derived stem cells	Animals	Tunica albuginea fibrosis decreased in a rat model of chronic PD.

PD, Peyronie's disease.

and immunosuppressive actions (*28*). In a previous study, ADSCs were injected shortly after TGF-β-induced tissue inflammation (during the acute phase), and this therapy reversed the phase of PD progression.

Another study evaluated the role of ADSC injection in the chronic phase of PD in a rat model (*36*). Rats with PD were injected with human ADSCs 1 month after injection of TGF-β1 (mimicking the chronic phase of PD), and they displayed less fibrosis on histological analysis, decreased expression of collagen III, and decreased expression of several fibrosis-related genes. All of these features are considered to be biochemical fibrotic changes. The same study also found that fibrotic plaques tended to partially regress spontaneously after 60 days. Two previous studies by Gokce *et al*. evaluated the efficacy of allogenic ADSCs and modified ADSCs expressing human interferon α-2b in the prevention and treatment of ED in a rat model of PD (*37,38*). In the first study (*37*), rats received intratunical injections of 0.5 million rat-labeled ADSCs on day 0 (prevention group) or day 30 (treatment group) after injection of TGF-β. Forty five days after treatment, both the prevention and treatment groups had better erections and less fibrosis compared to a group with untreated PD. The second study (*38*) compared the efficacy of modified ADSCs expressing human interferon α-2b and that of unmodified ADSCs using the same design as the previous study. Results indicated that modified ADSCs resulted in better recovery of erectile function.

The first study using placental matrix–derived mesenchymal stem cells (PM-MSC) to manage PD in humans involved a small sample of 5 subjects. Patients with PD with a palpable plaque received intracavernous injections of PM-MSC. Both peak systolic velocity and penile curvature improved significantly 6 weeks, 3 months, and 6 months after injection, but end diastolic velocity did not improve significantly. Seven of the 10 plaques initially evident on ultrasonography disappeared completely at 3 months (*39*). Results of animal and human trials demonstrating the possible efficacy of stem cell therapy in the treatment of PD are shown in Table 1.

4. Conclusion

Multiple studies have demonstrated the efficacy of stem cell therapy for the treatment of PD in humans and animals. Studies involving humans have been limited by their small samples and brief follow-up, but their results were promising. Randomized clinical trials in humans need to be conducted in order to prove the efficacy of stem cell therapy for the treatment of PD.

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Received November 24, 2019; Revised January 19, 2020; Accepted January 24, 2020.

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Released online in J-STAGE as advance publication February 4, 2020.