## ORIGINAL RESEARCH

# Intratunical Injection of Genetically Modified Adipose Tissue-Derived Stem Cells with Human Interferon α-2b for Treatment of Erectile Dysfunction in a Rat Model of Tunica Albugineal Fibrosis

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**ABSTRACT**

***Introduction.*** Peyronie's disease (PD) has frequently been associated with erectile dysfunction (ED) and may further compromise coitus.

***Aim.*** To investigate the efficacy of intratunical injection of genetically modified rat adipose tissue-derived stem cells (ADSCs) expressing human interferon α-2b (ADSCs-IFN) in decreasing fibrosis and restoring erectile function in a rat model of tunica albugineal fibrosis (TAF).

***Methods.*** A total of 36 Sprague-Dawley rats (12 weeks old; 300–350 g) were randomly divided in six equal groups: (i) sham group (50 μL saline-injected into the tunica albuginea [TA]); (ii) TAF group (transforming growth factor [TGF]-β1 [0.5 μg/50 μL] injected into the TA); (iii) TGF-β1 plus $5 \times 10^5$ control ADSCs injected same day; (iv) TGF-β1 plus $5 \times 10^5$ ADSCs-IFN injected same day; (v) TGF-β1 plus $5 \times 10^5$ control ADSCs injected after 30 days; and (vi) TGF-β1 plus $5 \times 10^5$ ADSCs-IFN injected after 30 days. Rat allogeneic ADSCs were harvested from inguinal fat tissue.

***Main Outcome Measures.*** Forty-five days following the TGF-β1 injection, erectile function was assessed, and penile tissues were harvested for further evaluations.

***Results.*** In the same-day injection groups, intratunical injection of ADSCs and ADSC-IFN improved erectile response observed upon stimulation of cavernous nerve compared with TAF group. Intratunical ADSC-IFN injection at day 30 improved erectile responses 3.1, 1.8, and 1.3 fold at voltages of 2.5, 5.0, and 7.0, respectively, when compared with TAF group. Furthermore, at voltages of 2.5 and 5.0, treatment on day 30 with ADSCs-IFN improved erectile responses 1.6- and 1.3-fold over treatment with ADSCs alone. Local injection of ADSCs or ADSCs-IFN reduced Peyronie's-like manifestations, and these effects might be associated with a decrease in the expression of tissue inhibitors of metalloproteinases.

***Conclusion.*** This study documents that transplantation of genetically modified ADSCs, with or without human IFN α-2b, attenuated Peyronie's-like changes and enhanced erectile function in a rat model of TAF. **Gokce A, Abd Elmageed ZY, Lasker GF, Bouljihad M, Braun SE, Kim H, Kadowitz PJ, Abdel-Mageed AB, Sikka SC, and Hellstrom WJ. Intratunical injection of genetically modified adipose tissue-derived stem cells with human interferon α-2b for treatment of erectile dysfunction in a rat model of tunica albugineal fibrosis. J Sex Med 2015;12:1533–1544.**

***Key Words.*** Tunica Albuginea; Fibrosis; Stem Cells; Human Interferon α-2b; Gene Therapy; Erectile Dysfunction; Peyronie's Disease

 

## Introduction

Peyronie's disease (PD) is a fibrotic wound-healing disorder of the penis characterized by plaque formation in the tunica albuginea (TA). It can be both a physically and psychologically debilitating condition for the afflicted man, and also affect his partner. Despite PD being recognized by the medical community for more than 250 years, it remains a therapeutic dilemma due to an incomplete understanding of its pathophysiology and the relative paucity of randomized, placebo-controlled trials [1]. Although there are many theories as to the etiology of PD, most authorities postulate that PD results from repetitive minor trauma to the penis during intercourse with subsequent abnormal wound healing and scar formation [2]. There is a localized disruption of the penile TA and an increase in microvascular permeability with release of various cytokines and growth factors following injury to the erect penis [3]. Current literature highlights the role of cytokine release, primarily transforming growth factor β1 (TGF-β1), as the predominant pro-fibrotic factor in the development of PD [2,3]. TGF-β1 is a cytokine that is an endogenous mediator of most fibrotic processes and abnormal wound healing. The TGF-β1 rat model for PD was first proposed by Dr Tom Lue in the late 1990s [4]. This model has distinctive advantages in the studies of PD due to its ability to induce chronic inflammation and fibrosis in the TA over time with only a single injection of the compound. The most important disadvantages of this model relates to the inconsistencies in timing and duration of the fibrotic plaque following the local injection of TGF-β1 [3].

The pro-fibrotic role of TGF-β1 in the pathophysiology of PD has led to several pharmacological applications such as using interferons and phosphodiesterase 5 inhibitors. Although many nonsurgical treatments have been promoted, none offer a reliable and effective correction of the penile deformity, and for this reason, surgery remains the gold standard [5,6]. Recently, clostridium histolyticum collagenase (Xiaflex, Auxilium, Chesterbrook, PA, USA) has been approved by the Food and Drug Administration for this indication. However, since most patients present clinically in the advanced/chronic phase, the success of this modality is not foolproof.

Stem cell-based therapies have documented benefit in the prevention of ED following cavernous nerve injury in an animal model [7]. Recently, adipose tissue-derived stem cells (ADSCs) have become a valuable resource because of their abundance and ease of isolation [8]. Several investigators have reported that mesenchymal stem cell transplantation can significantly decrease fibrosis in the heart, lung, kidney, and liver [9–12]. Moreover, in a previous study, the preventative benefits of ADSCs on tunica albugineal fibrosis (TAF) and ED have been demonstrated in the acute/inflammatory phase when compared with the chronic phase in an animal model [13]. Previous studies also showed that intralesional injection therapy with IFN α-2b demonstrated beneficial effects on PD [14]. The main disadvantage of this treatment modality is the need for repeated injections.

## Aims

The current study aimed to investigate the efficacy of intratunical injection of genetically modified rat ADSCs expressing human interferon α-2b (ADSCs-IFN) in decreasing fibrosis and restoring erectile function in a rat model of TAF.

## Methods

### *Study Design*

Male Sprague-Dawley rats (12 weeks old; 300–350 g) were purchased from Harlan Laboratories (Indianapolis, IN, USA) and housed in a regulated environment with a 12-hour light/dark cycle in a standard experimental laboratory of Tulane University. The animals had free access to food and water ad libitum. A total of 36 male Sprague-Dawley rats (12 weeks old; 300–350 g) were randomly divided into six equal groups: (i) sham group (50 μL saline-injected into the TA); (ii) TAF group (0.5 μg/50 μL TGF-β1 injected into the TA); (iii) TGF-β1 plus $5 \times 10^5$ control ADSCs injected same day (ADSCs prevention group) (iv) TGF-β1 plus $5 \times 10^5$ ADSCs-IFN injected same day (ADSCs-IFN prevention group); (v) $5 \times 10^5$ control ADSCs injected 30 days after TGF-β1 injection (ADSCs treatment group); and (vi) $5 \times 10^5$ ADSCs-IFN injected 30 days after TGF-β1 injection (ADSCs-IFN treatment group). Rat allogeneic ADSCs were harvested from inguinal fat tissue. Forty-five days following TGF-β1 injection, all rats underwent evaluation of erectile function; the rats were sacrificed, and the penile tissues were harvested and stored at –80°C for further analysis. All experiments were performed according to the Guidelines for the ethical conduct in the care and use of