

A Review: Regenerative Strategies for Testicular Rejuvenation Using Stem Cells, Exosomes, and Platelet Rich Plasma (PRP)

Panayiotis Michael Zavos^{1*}, Carmen Navarro² and Theodora Maria Zavos³

¹Director and Chief of Andrology, Andrology Institute of America Lexington, Kentucky USA.

²REI, Women Fertility Center and Women Care Center Caracas, VENEZUELA.

³Visiting Scholar, Andrology Institute of America Lexington, Kentucky, USA.

*Correspondence:

Panayiotis Michael Zavos, Director and Chief of Andrology, Andrology Institute of America Lexington, Kentucky USA.

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Platelet Rich Plasma (PRP), Stem cells, Hypogonadism.

Introduction

Testicular rejuvenation represents a novel and evolving area within regenerative medicine aimed at restoring the functional capacity of the testes in men suffering from impaired spermatogenesis, hormonal insufficiency, or testicular degeneration. Conditions such as non-obstructive azoospermia, Sertoli-cell-only syndrome, and primary testicular failure can severely compromise male fertility and androgen production. Traditional treatments have offered limited success, particularly in cases with intrinsic testicular damage. In response, regenerative approaches, including the use of stem cells, extracellular vesicles such as exosomes, and platelet-rich plasma (PRP) have emerged as promising modalities. These biologics harness the body's inherent repair mechanisms to restore the testicular microenvironment, promote cellular regeneration, and potentially reactivate dormant spermatogenic pathways. With increasing preclinical and early clinical evidence supporting their efficacy, testicular rejuvenation therapies may redefine future strategies in the management of male infertility and hypogonadism.

Stem Cell Based Therapeutics

Mesenchymal stem cells (MSCs) have gained attention for their ability to modulate the testicular microenvironment via immunomodulatory and trophic effects. A Phase I clinical trial involving autologous bone marrow derived MSCs (BMMSCs) delivered via microsurgical testicular sperm extraction (MicroTese) demonstrated that among men with NOA, 22.5% of those with secondary infertility achieved improved hormonal profiles and sperm production six months posttreatment, with no adverse events reported [1,2]. In another study involving 87 NOA patients treated

with intratesticular BMMSC injections, approximately 20.7% developed detectable sperm in semen over time, accompanied by improvements in libido and hormonal parameters [3].

Preclinical evidence further substantiates these findings. In rat models of testicular torsion and ischemia-reperfusion, intratesticular BMMSC administration led to significantly higher Johnsen scores, indicating better preservation of spermatogenesis, along with elevated anti-inflammatory cytokines (e.g., IL10) and reduced oxidative markers [4]. Similarly, human umbilical cord derived MSCs transplanted into hypogonadism models generated Leydig cells expressing steroidogenic markers and restored serum testosterone levels [5].

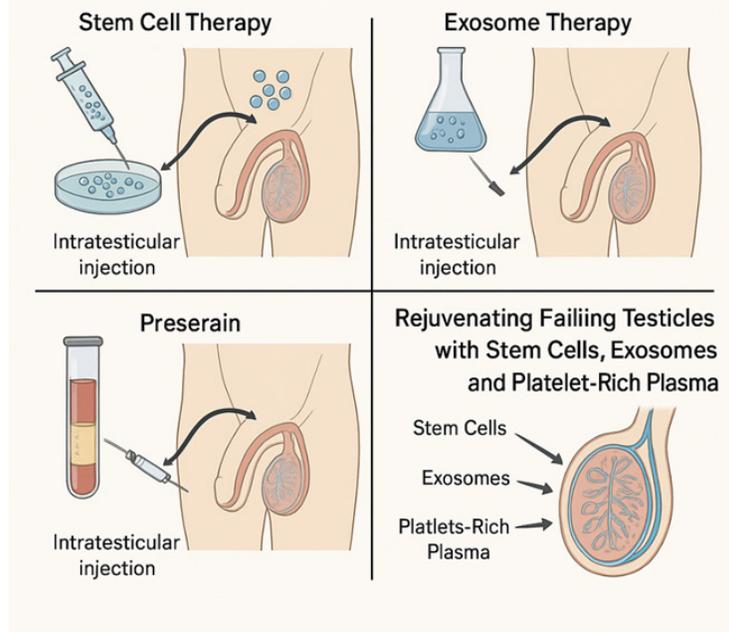
Exosome Therapy

Exosomes, nanoscale extracellular vesicles secreted by MSCs and other stem cell types, have emerged as promising agents for regenerative signaling. In aged mice, intratesticular injection of human umbilical cord MSC-derived exosomes (hUMSCExos) markedly reduced apoptosis, promoted macrophage polarization toward the M2 phenotype, attenuated oxidative stress, enhanced spermatogenic recovery, and elevated testosterone synthesis [6]. Mechanistic in silico analyses support the interaction between BMMSC exosomal protein cargo and spermatogenic cell surface receptors, suggesting a paracrine mechanism underlying functional testicular regeneration [2].

Platelet Rich Plasma (PRP) Applications

Platelet rich plasma (PRP), an autologous concentrate enriched with growth factors such as VEGF, IGF1, PDGF, EGF, and TGF β , has been investigated for its potential in male reproductive regeneration. In a controlled experimental model of testicular

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torsion in rats, intratesticular PRP resulted in significantly higher Johnsen scores compared to saline controls ($P < 0.001$), along with lower LH and higher testosterone levels, suggesting enhanced Leydig cell function and seminiferous tubule recovery [7].

In humans, a prospective cohort study of 135 men with NOA and prior failed microTESE found that intratesticular PRP injections yielded sperm retrieval rates of 27.5% in those with one prior failure and 16.4% in men with two or more failures. IVF outcomes were favorable, with fertilization rates reaching up to 100% and pregnancy rates per embryo transfer of 36.8% and 22.2% respectively [1]. A systematic review of human studies similarly concluded that PRP may improve semen parameters, reduce DNA fragmentation, enhance cryopreservation recovery, and increase surgical sperm retrieval success in male factor infertility—though acknowledged the need for better designed trials [8].

Integrated Regenerative Protocols

Contemporary investigational protocols are exploring combinatory use of MSCs, exosomes, and PRP to leverage synergistic mechanisms: cellular support from MSCs, signaling molecules from exosomes, and growth factor-mediated trophic stimulation from PRP. While specific clinical trials employing all three together remain limited, *in silico* and preclinical models support the plausibility of cocktail strategies that combine cellular, paracrine, and growth factor modalities [2,6,9].

Spermatogonial Stem Cell (SSC) Transplantation

The first human Spermatogonial stem cell transplantation was performed in a cancer survivor who had earlier preserved immature testicular tissue. Autologous SSCs were reintroduced into the rete

testis under ultrasound guidance. Although no sperm has yet been detectable, testicular histology remained intact, and the procedure is being monitored biannually. This landmark case follows success in animal models and underscores the translational potential of SSC transplantation for prepubertal cancer survivors and men with testicular failure [10].

Adjunctive and Supportive Measures

Adjunctive strategies are often used to enhance regenerative outcomes, including hormonal priming with clomiphene or hCG to improve testicular receptivity. Antioxidant supplementation (e.g., coenzyme Q10, vitamin E, Lcarnitine) may reduce oxidative damage and support mitochondrial function, as shown in rodent torsion models [11]. Preclinical evidence suggests that hyperbaric oxygen therapy and low intensity shockwave therapy may further stimulate angiogenesis, stem cell homing, and regenerative capacity.

Clinical and Ethical Considerations

Despite promising data, these modalities are largely investigational, lacking standardized protocols or regulatory approval in most jurisdictions. The safety of repeated intratesticular injections remains uncertain, with potential risks including fibrosis or unwanted cellular proliferation. Moreover, exosome preparations vary widely in purity and potency, requiring rigorous quality control [12]. SSC transplantation procedures remain in early phases, and long-term safety validation is pending. Consequently, all regenerative protocols should be conducted under IRB approved clinical research frameworks, with informed consent and ethical oversight.

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