REVIEWS

ADIPOSE DERIVED MESENCHYMAL STEM CELLS RESTORE SPERMATOGENESIS IN MALE NON OBSTRUCTIVE AZOOSPERMIA (LITERATURE REVIEW)

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Stem cells are considered as new much promising therapeutic agents in treatment of male infertility due to their high differentiation potential and unlimited supply. In this review we summarized current views on application of mesenchymal stem cells in reproductive medicine.

Key words: assisted reproductive technologies; male infertility factor; non obstructive azoospermia; mesenchymal stem cells; adipose tissue, bone marrow

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INTRODUCTION

In the recent years, the emerging field of stem cell therapy has opened a new era of regenerative medicine. Being a totally new approach in the treatment of various diseases the diverse potential of stem cells is in a focus of research of many scientists in molecular biology, genetic engineering and general medicine [1].

Stem cells have the ability of self-sustaining throughout the life and are capable of differentiating into cells of various lineages. There are several types of stem cells found in human tissues [2]. Among them, mesenchymal stem cells (MSCs) derived from bone marrow and adipose tissue are considered to be successful in terms of their application for cell therapy. MSCs are multipotent human stromal stem cells able to self-renew. The general properties of MSCs include: high proliferative potential, adhesion to plastic, symmetric and asymmetric division, fibroblast-like morphology, easily induced differentiation, and formation of colonies in a culture [3-5].

MSC were first described by Friedenstein et al [6-7] demonstrating the existence of stromal stem cells in bone marrow and lymphoid organs. Their discovery confirmed that the bone marrow contained a distinct population of stem cells capable of forming clones of connective and hematopoietic cell lines. Approximately 30% of the bone marrow aspirate isolated by this team consisted of MSC. These cells showed plastic adhesion capacity and were able to differentiate into chondrocytes, fibroblasts, adipocytes and myoblasts [8-11]. Thus they have been classified as multipotent cells. Their therapeutic effect is based on the ability to secrete a number of signal molecules that modulate functions of various cells in human body [12].

MSCs promote growth of hematopoietic progenitors thus creating specific microenvironment (niche) and facilitating migration of hematopoietic stem cells (HSC) [13-15]. MSCs express a number of markers, including: STRO-1, Sca-1, SH-2, SH-3, SH-4, Thy-1, CD29, CD44, CD71, CD120a, CD106, CD124.

MSCs represent a rather dynamic system in the bone marrow, which consists of differentiated fibroblasts, endothelium, cytokines, reticular cells, and components of the extracellular matrix. Cell interactions within the same lineage and with adjacent ones occur through adhesion molecules and specific receptors [16].

MSCs are popular amongst scientists and clinicians due to their differentiation potential, low immunogenicity, and active participation in tissue repair and regeneration after migration to damaged sites [17]. For a long period, MSC isolation was considered as technically difficult due to traumatic specifics of fat removal and bone marrow aspiration [18-20].

Bone marrow is the main source of MSCs, and their aspiration still represents the most traumatic link in the chain of the whole MSC isolation procedure. The MSC number, differentiation potential and the viability of bone marrow MSCs (BM MSC) demonstrate the age-related decrease [21]. In this regard, the ongoing search for alternative sources of MSC continues. MSCs derived from adipose tissue (AT MSCs) can be alternative solution for BM MSCs due to their comparable differentiation and therapeutic potential [13].

Adipose tissue is not only a metabolic reservoir for storage and formation of high-energy substrates; it also participates in hormone metabolism [22]. A more profound study of the adipose tissue structure was performed by M. Rodbell; using techniques of proteolytic cleavage, mechanical grinding and differential centrifugation, 2 fractions of adipose tissue were isolated. These included mature adipocytes and more condensed cellular substance, which was later denominated by Rodbell as a stromal-vascular fraction (SVF). SVF is heterogeneous and contains blood cells, pericytes, endothelial cells, fibroblasts,

and pre-adipocytes [23]. Studies have shown that SVF is a huge reservoir of MSC. In 2001 Zuk et al. noted that properties of so-called Adipose Derived Stem Cells (ADSCs) were similar to bone marrow mesenchymal stem cells [24-25]. In an adult bone marrow, the proportion of MSCs is 1:50000 to 1:1000000 cells, whereas in adipose tissue, the ratio of MSCs is 1 per 30–1000 cells [26].

AT MSCs are easier and safer to obtain. The primary acquisition of AT MSC is based on the manually performed procedure including the lipoaspirate (LA) fermentation technique [27]. Adipose tissue suitable for MSC isolation can be obtained either by resection of lipodermal skin flaps or by liposuction (LS) [28-34].

Many scientists chose LS as a surgical intervention preferable for aspirating adipose tissue suitable for isolation of MSCs. Due to the little traumatic impact of this operation, no long-term postoperative rehabilitation of patients is required. Currently, there are various techniques for LS implementation as new state-of-theart equipment continues to emerge (ultrasound, laser) [35]. The most popular option though, is classical tumescent LS, where fat tissue in the donor area of the patient's body is infiltrated with a mixture of sterile saline with low concentrations of local anesthetic and epinephrine [36]. The LS technique can affect both the viability and quantity of MSCs isolated from fat tissue. With classical LS, the negative pressure in the aspirator is reversely proportional to the number of isolated stem cells [37]. According to Matsumoto et al. [20], when this type of surgical intervention is applied, stem cells should be processed no later than 1 day after the extraction of the fat material from the body, since storage of the fatty substrate at a room temperature decreases number of viable stem cells. Small portions of autologous adipose tissue extracted from the patient's body with a syringe are easily processed for MSC isolation, whereas processing of a large volume of aspirated fat is associated with certain difficulties [38]. Currently, researchers use a number of modified original techniques for adipose stem cells isolation [19,39-40]. With classical liposuction, the aspirate is separated into 3 layers: (i) the top fatty layer containing homogenized mature adipocytes destroyed during the operation; (ii) the middle layer of intact adipose tissue and (iii) the bottom layer containing residuals of the solution infiltrated into the patient's tissue before surgery with plasma and blood cells. Both the top and bottom layers are removed from the container before aspirated fat processing [41]. The remaining middle layer is washed with sterile phosphate buffer with added antibacterial and antimycotic agents to avoid microbial contamination of the material [18, 28, 42]. Next, the adipose tissue is lysed in sterile collagenase solution to release the components of the stromal vascular fraction (SSF) containing stem cells [43, 44]. Different type enzymes are used, but type IA collagenase is the most effective for MSC isolation [27, 28, 42].

In 2001, the Zuk's team [27] successfully cultured and studied multipotent cells isolated from human autologous adipose tissue (AAT). Following their success, scientists began to search for ways to safely aspirate fat tissue from patients, isolate and cultivate stem cells [30, 32, 35, 37, 41, 45]. There are many reports suggesting effective application of MSCs both in experimental animals and small groups of patients. Currently, wide use of MSC in clinical practice is limited by safety considerations. Despite large numbers of registered preclinical and clinical studies, the safety of MSC-related therapies remains the major concern for clinicians. The main risks of mesenchymal stem cells are proinflammatory properties, tumorigenicity, and fibrosis. Tumorigenicity is one of the most serious ones. On the one hand, MSCs have the ability to converse into tumors, some studies showed that Ewing's sarcoma cells originate from MSCs [46], on the other hand, MSCs can trigger tumor development. MSCs overproduce cytokines, such as growth factors and chemokines, directly acting on surface receptors of cancer cells, thereby regulating tumor enhancement. Immunosuppressive ability of these cells also promotes growth and metastasis of cancer cells [47,48]. Another feature of MSCs contributing to tumor development is their pro-angiogenic [49]. MSCs exhibit immunosuppressive effects when exposed to sufficiently high levels of proinflammatory cytokines. However, they promote inflammatory responses in the presence of low levels of IFN-γ and TNF-α [49]. This indicates that MSCs must be triggered by inflammatory cytokines to become immunosuppressive, and the inflammatory environment is a critical factor influencing the immune regulation of MSCs. To improve therapeutic effects of MSCs and reduce potential risks, further studies are needed to investigate immunomodulatory effects of MSC, control excessive cytokines, and establish strict standards for preclinical biosafety tests [50].

Some studies indicate that embryonic stem cells very similar to MSCs have been found in the testes [50]. These cells are located in the basal layer of the testicular seminiferous tubules, they can divide asymmetrically and grow into progenitor cells. These cells survive chemotherapy and can trigger germinative cell differentiation. They, therefore, serve as a reserve storage for stem cell population [51]. It is likely that the interaction between these cells and the transplanted MSC plays a crucial role in the fertility restoration.

AZOOSPERMIA: CAUSES, CLASSIFICATION AND MECHANISMS

According to WHO criteria [52], the marriage is considered infertile if no pregnancy occurs within 12 months of unprotected sex. This pathology is an important medico-social issue with up to 15% (one in six) of married couples failing to conceive naturally [53-55]. Amongst them, in 45-50% infertility is caused solely by impaired spermatogenesis [56]. Both for spouses and their doctors, a diagnosis of infertility is a beginning of the long way of tests and possibly therapy. Fertility problem is diagnosed in 5-7% of men; 50-60% of infertility cases are linked to the reduced quantity or quality of ejaculate, which may be due to impaired spermatogenesis, slow maturation of spermatozoa in the epididymis or incomplete patency of *vas deferens* [56-61]. The main causes of male infertility are genetic disorders, urogenital infections, hypogonadism, cryptorchidism, varicocele, ejaculatory disorders, general and systemic diseases, immunological factors [62]. Despite its multifactorial nature, male infertility is not yet fully understood with about half of cases considered to be idiopathic or unexplained [63]. Investigation of male fertility usually starts with history, physical examination, and spermogram. In about 15% of patients, spermogram shows no obvious abnormalities [64]. However, it has been shown that sperm cells in infertile men have lower DNA integrity than in fertile ones [35,65-66]. This is very important, because the genetic information passed on to the next generation, depends on the integrity of the sperm DNA [67]. Since several etiological factors contribute to the defective sperm count, the assessment of sperm DNA fragmentation (SDF) may provide an opportunity to better understand and treat such sperm disorders [67].

Table 1. Summary of the Relevant Studies

Type of Cell in Study	Cell Surface Character	References
Multipotent mesenchymal stromal cells	These must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules	[121]
Adult human bone marrow stromal stem cells	xpress telomerase activity in vivo	[122]
Mesenchymal stem cells	Cells were negative for hematopoietic markers (CD14, CD34, CD45) but positive for markers present in mesenchymal cells CD13, CD29, CD90	[123]
Mesenchymal stem cells	Found a population of CD34 and CD45 negative cells which were positive for CD44, CD73 and CD105	[124]
Human adipose tissue-derived stromal cells	CD9, CD10, CD13, CD29, CD34, CD44, CD 49(d), CD 49(e), CD54, CD55, CD59, CD105, CD106, CD146, and CD166. But no STRO-1 antigen was found as in human adipose tissue derived stromal cells	[125]
Multipotent mesenchymal stem cells	Positive for SH2, SH3, SH4, CD29, CD44 and HLA-ABC (MHC class I), low positive for CD90 and CD105, but negative for CD10, CD11b, CD14, CD34, CD117, HLA-DR, DP, DQ (MHC class II) and EMA	[126]
Mesenchymal precursor cells found in the blood	A minority of adult marrow cells express CD34 BMPCs stained strongly with anti-CD44 antibody. Conventional T-cell (CD3), monocyte (CD14, CD68), and B-cell (CD20) antibodies stained neither of the two BMPC populations, nor did they react to anti-LCA (CD45), antiVCAM (CD106), or MHC-Class II (anti-DR) [49]	[127]
Placenta-derived mesenchymal progenitor cells (PDMPC)	The PDMPC expressed CD13, CD44, CD73, CD90, CD105 and HLA class I as surface epitopes, but not CD31, CD34, CD45 and HLA-DR.	[128]
Mesenchymal stem cells	Cells expressed CD29, CD44, CD71, CD90, and CD105/SH2 and SH3, expressed STRO-1. No expression of CD31, CD34, and CD45. Positive expression of CD13 and the absence of CD14, CD16, CD56, CD61, CD62(e), CD104 and CD106. CD49(d) was not observed in MSC culture. However MCS expressed CD106 antigen.	[129]
Stem cells from human exfoliated deciduous teeth (SHED)	SHED were found to express the cell surface molecules STRO-1 and CD146, which are cell surface markings of adult bone marrow-derived stromal stem cells.	[130]
Putative stem cells of menopausal human ovarian surface epithelium	Pluripotent gene transcripts Oct-4, Oct-4A, Nanog, Sox-2, TERT, Stat-3 in human.	[131]
Human bone marrow-derived mesenchymal stem cells	CD29, CD44, CD90 and CD90	[132]
Dermal tissue stem cells	Express CD44, CD54, CD90, CD105 and CD271 which are stem cell markers.	[133]
Adipose-derived stromal/stem cells	CD29(+) CD34(+) CD44(lo) CD45(low) CD73(+) CD90(+) CD105(+)	[134]
Mesenchymal stem cells	STRO-1 positive	[135]
Multipotent endometrial stromal cells and multipotent decidual stromal cells	Express surface molecules CD73, CD90 and CD105	[136]
Mesenchymal stem cells	CD105, CD90 and CD73.	[137]
Mesenchymal stem cells	Expression of CD105, CD166 and CD44, and the absence of CD45, CD34 and CD14 on the surface of mesenchymal stem cells like cells	[138]
Mesenchymal stem cells from human skin biopsies (S-MSCs)	Expression of HLA-A, B, C, CD29, CD44, CD73 and CD90, was strongly positive, while CD105 was low positive, and CD10, CD11b, CD14, CD34, CD49d and HLA-DR were negative	[139]
Mesenchymal stem cells in bone marrow	CD13, CD15, CD73, CD140b, CD144, CD146 and CD164	[140]
Mesenchymal stem cells and human cardiac valve ICs (interstitial cells)	Expressed fibroblast surface antigen, smooth muscle alphaactin, vimentin and CD44. CD105 was weakly expressed by MSCs (>90%).	[141]

Table 1. (Contd.)

Bone marrow derived stromal progenitor cells	STRO-1 positive	[142]
Stromal cells derived from the bone marrow	STRO-1 positive	[143]
Bone marrow-derived mesenchymal stem cells	STRO-1 positive	[144]
BM-derived mesenchymal stem cells	STRO-1 positive + CD34 positive STRO-1 positive, CD34 positive	[145]
Bone marrow derived mesenchymal stem cells	CD106 positive, CD34 positive	[146]
Bone marrow-derived mesenchymal stem cells	STRO-1 positive	[147]
Human bone marrow mesenchymal progenitor cells	Express integrin subunits alpha4, alpha5, beta1, integrins alphavbeta3 and alphavbeta5, ICAM-1, and CD44H. These were CD49d (-) and CD34 (-)	[148]
Adult human mesenchymal stem cells	CD49d (-), CD106 (+), CD34 (-)	[149]

Azoospermia is classified as obstructive and non-obstructive [68]. In most patients with non-obstructive azoospermia, it is possible to distinguish both clinically by thorough diagnostic workup (history, hormone levels, physical examination). These indicators help to determine with high confidence the type of azoospermia [68]. This is important, since obstructive azoospermia is more favorable due to preservation spermatogenesis [69-70].

Non-obstructive azoospermia (NOA) accounts for 5-10% of infertility cases. It manifests as absence of spermatozoa in ejaculates due to spermatogenic deficiency [71]. In the overwhelming majority of cases, azoospermia is associated with a number of irreversible disorders of the testicles, which lead to inhibition of spermatogenesis [71]. Such disorders are most often linked to endocrine, genetic and inflammatory diseases. Also, non-obstructive azoospermia can be idiopathic [84].

Non-obstructive azoospermia should be thoroughly ruled out in all azoospermic patients [72-73]. Palpation and measurement usually reveals small and flabby testicles typical for non-obstructive azoospermia. About 85% of the testicular parenchyma is involved in spermatogenesis; the smaller the testes, the less sperm is produced [68,72]. Based on this, such patients should always have an ultrasound scan of scrotum also to rule out varicose veins of the spermatic cord [74].

In all patients with azoospermia, the levels of FSH, LH, prolactin [72], total testosterone, estradiol, inhibin B should be measured. In most patients with nonobstructive azoospermia, FSH will be increased (> 7.6 IU/ml) [72,75,76], and LH is elevated or close to normal. Since negative correlation of FSH and LH secretion is determined by the number of Leydig cells and spermatogonia, the levels of FSH and LH may be normal [77].

Hypogonadism is defined by low total testosterone levels (<300 ng/dL) and occurs in the majority of patients with non-obstructive azoospermia, usually reflecting Leydig cell deficiency [78-80].

Obesity can be associated with low total testosterone levels, thereby serum estradiol levels increase due to elevated aromatization of androgens in peripheral tissues [81-83]. Low testosterone in obese patients may also reflect adaptation to altered SHBG, rather than true testosterone deficiency [84]. Therefore, it is necessary to assess both estradiol and SHBG in patients with azoospermia and obesity. Estradiol > 60 pg/ml suppresses LH and FSH secretion and directly inhibits testosterone biosynthesis [81]. These tests can help to decide the treatment strategy before a testicular biopsy is implemented. Due to daily fluctuations in testosterone levels, blood samples are collected before 10:00 am [78, 81].

Proper counseling and management of patients with non-obstructive azoospermia presents a challenge for andrologists, urologists, and reproductive medicine specialists. Despite this, advances in molecular biology, hormone replacement therapy, and microsurgical sperm retrieval, together with modern techniques of in vitro fertilization (IVF), give hope for natural paternity [71]. Due to irreversible nature of spermatogenesis damage in patients with non-obstructive azoospermia, testicular biopsy and assisted reproductive technologies are the only ways to obtain biological off-springs.

Non-obstructive azoospermia is considered to be a condition not responding to drug therapy [71]. Patients with non-obstructive azoospermia are unable to have children of their own and have options of either adoption or using donated sperm [85]. Despite the marked changes in spermatogenesis, these patients still have a chance to conceive. In such situations, the preservation of spermatogenesis may be focal and present in 10% –50% of testicular tissues [86,87]. For men with non-obstructive azoospermia, testicular sperm extraction (TESE) with intracytoplasmic sperm injection (ICSI) remains the only choice to conceive [88]. However, TESE-ICSI has limited success in patients with non-obstructive azoospermia, as during the first TESE cycle, sperm is found only in 56% of cases, and the subsequent probability of egg fertilization with ICSI is only 41%. As a result, the successful fertilization probability with this technique is only 23% [88]. Advances in assisted reproductive technologies such as intracytoplasmic sperm injections and in vitro fertilization have changed the treatment strategies of non-obstructive azoospermia management [89]. Obtaining spermatozoa is possible only through testicle biopsy, with the subsequent intracytoplasmic injection of sperm into an egg (ICSI) [73, 86, 87, 90]. Treatment of patients with this form of infertility is the most difficult from a psychological and clinical point of view [54, 55, 91].

ADIPOSE DERIVED MESENCHYMAL STEM CELLS IN TREATMENT OF NON OBSTRUCTIVE AZOOSPERMIA

In recent years, a significant progress has been achieved in the treatment of assisted reproductive diseases, and now more than 80% of infertile couples can have children [92]. Due to their unlimited source and high differentiation potential, stem cells are considered as potential new therapeutic agents for the treatment of infertility.

MSC transplantation is a relatively new therapy proposed to induce spermatogenesis and treat male infertility [93]. Since MSC are involved in processes such as cell survival, proliferation, migration, angiogenesis, and immune modulation, these cells are considered as an ideal material.

Germinal cells are the conserved embryonic stem cells, these cells provide spermatogenesis [94]. It is likely that the interaction between these cells and the transplanted MSCs plays a role in the restoration of fertility. A certain combination of growth factors can be used to induce the differentiation of MSCs into cells of the germ cell epithelium [95-96]. Nayernia et al. demonstrated for the first time that rat bone marrow MSCs could differentiate into male germ cells [97].

Yazawa et al. proved that spermatogonial stem cells were able to differentiate into steroidogenic cells, such as Leydig cells, both in vivo and in vitro [98]. BM MSCs transplanted into testes of busulfan-induced azoospermic rats, promoted differentiation into Sertoli and Leydig cells [99]. In one study [100], MSCs derived from perivascular cells of the human umbilical cord were able to differentiate into germ cell-like cells exposed to a cocktail of growth factors such as leukemia inhibiting factor (LIF), glial neurotrophic factor (GDNF), retinoid acid, testosterone, and follicle-stimulating hormone. Fluorescence *in situ* hybridization (FISH) also showed that 10% –30% of cells gave rise to haploid cells. The results obtained in the expression analysis evidenced that these cells could produce Sertoli-like cells under the same conditions [101]. These observations suggest that the functioning of similar signaling pathways promotes the development of Sertoli cells and germ cells. Asgari et al. found that factors secreted by Sertoli cells could lead to the differentiation of MSCs into primary germ cells (PGCs) [101]. This model of morphology and expression of MSC, co-cultured with Sertoli cells, was similar to germ cells, confirming their differentiation into male cells [102]. Results of preclinical trials have demonstrated that fertility can be restored through MSC transplantation. In 2012, Sabbaghi et al. transplanted BM MSCs into the testes of rats with azoospermia modeled by testicular torsion. However, the markers expression of germ cell epithelium showed differentiation into germ cells [103]. Transplantation of MSCs into convoluted tubules of rats with busulfan-induced azoospermia helped to restore spermatogenesis [104-106]. BM-MSC transplantation improves expression of germ cell markers in the testes and can be proposed as a suitable method for the treatment of infertility. According to many researches, the increased expression of testicular germ cell markers after BM-MSC transplantation enables to suggest this method for treatment of male infertility [105,107]. Moreover, MSCs may be involved in the suppression of antisperm antibodies (ASA) [108] and can reduce factors that lead to infertility caused by testicular torsion through reduction of apoptosis and oxidative stress and stimulation of testosterone production [109]. Ghasemzadeh-Hasankolaei et al. transplanted BM MSCs into testes of infertile rats and observed their differentiation in spermatogonia [110]. This study demonstrated improved differentiation capacity of MSCs, potentially leading to more remarkable restoration of testes ability to spermatogenesis compared to hematopoietic stem cells [110]. They found a substantial elevation of mRNA in three meiosis genes 6 weeks after injection of umbilical cord blood stem cells. The injection method was attributed to the ability of MSCs to differentiate in spermatogonia and other supporting spermatogenesis cells by increasing regulation of gene expression in spermatogenesis [111]. Fertility in male rats with busulfan-induced azoospermia was restored by transplantation of adipose tissue (AT) MSCs [106]. Cells with a green-fluorescent protein as a surface marker have been found on both sides: outside the basement membrane and inside the convoluted tubules. This confirms the idea that MSCs can participate in spermatogenesis in two ways: by supporting spermatogonial stem cells (SSCs) and differentiating into spermatozoa. Cord blood MSC transplantation is an effective method for increasing expression of germ cell stem cells in busulfaninduced azoospermic models [112]. The differentiation of AT MSCs into testicular germ cells suggests that cell therapy can help reverse pathological changes in the testicular convoluted tubules. AT MSCs recreate the microenvironment of the convoluted tubules through production of germ cells in the recipient's seminiferous tubules [106]. Monsefi et al. showed that transplanted AT MSCs can differentiate into germ cells in the convoluted tubules of Wistar rats. It was found that both AT MSC and BM MSCs are effective in treatment of azoospermia in animals. Successful spermatogenesis was achieved in guinea pigs with busulfan-induced azoospermia following injection of BM MSCs [113]. Allogenic AT MSCs could differentiate into cells similar to spermatogenic epithelium in vitro, providing theoretical and experimental background for clinical use of AT MSCs in treatment of infertility in animals such as guinea pigs with azoospermia [114]. In rats, BM MSCs mitigate the toxic effect of cisplatin on testes at both genetic and molecular levels [113]. Currently, 3 possible mechanisms of testicular function restoration during MSC-induced tissue regeneration are investigated: 1) MSCs can differentiate into target cells [115]; 2) the transplanted cells secrete growth factors, stimulating restoration of the recipient's cellular function [116] 3) MSCs connect with endogenous cells, restoring the function of damaged cells [117]. Sertoli cells are immunotolerant [117] and this, possibly, contributes to the protection of transplanted allogeneic cells from a post-transplant inflammatory or immune response, and the survival of donor BM MSCs. H. Chen et al. showed that sperm differentiation is possible after transplantation of cord blood MSCs into the testicular convoluted tubes in immunodeficient rats [118].

In 2016, scientists from Jordan presented observational data of patients who were given intratesticular injections of CD34/ CD133 cells.

CD34 - the absolute number of hematopoietic stem cells

CD133 - prominin-1 is a glycoprotein encoded in humans by the PROM gene.

These patients were followed up 5 years post-transplantation. No complications were recorded. 27 histological changes were found in 9 patients (33%). In 7%, growth of spermatids in the testes was confirmed, in 11% mature sperm was detected on spermograms. Spermatocytes and spermatozoa after stem cell transplantation appeared in 26%. Long-term observations recorded 6 natural conceptions, 2 births and 1 successfully performed IVF in three married couples [119]. In another study,

6 patients with nonobstructive azoospermia with negative results of microsurgical sperm extractionand levels of FSH > 25 mlU/ml (norm 1.4-13.6 mU/L) and inhibin B <16 (norm 148365 ng/ml) received intra-testicular injections of autologous MSCs. All patients showed a positive hormonal response. During treatment, the concentration of FSH reduced to 16.3 ± 5.6 mlU/ml, and inhibin B increased to 14.5 ng/ml. MicroTESE detected Germinogenic cells in 3 patients. Pregnancy was reported in two couples, one terminated at week 12 and another had 7-month normal development [120].

The presented data prove the great potential of MSCs in restoration of fertility in patients with non-obstructive azoospermia. Mastering and successfully applying this technique in clinical practice can help a vast group of patients to revive spermatogenesis and enjoy fatherhood.

Table 1 summarizes results of relevant studies.

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. *Yastrebov, A. P., Grebnev, D. Y., & Maklakova, I. Y.* (2012). Experimental substantiation of implementation of combined transplantation of stem cells for correction of regeneration of fast renewing tissues after radiation damage. Vestn. Ural. Med. Akad. Nauki, **2**, 39.
2. *Loseva, E. V.* (2001). [Neurotransplantation of the fetal tissue and compensatory-restorative processes in the recipient nervous system]. Uspekhi Fiziologicheskikh Nauk, **32**(1), 19–37.
3. *Gonzaga, V. F., Wenceslau, C. V., Lisboa, G. S., Frare, E. O., & Kerkis, I.* (2017). Mesenchymal Stem Cell Benefits Observed in Bone Marrow Failure and Acquired Aplastic Anemia. Stem Cells International, **2017**, 8076529. DOI: 10.1155/2017/8076529
4. *Mikhailichenko V.Yu., Samarin S.A., Estrin S.I.* Comparison of the Cardiomyogenic Potency of Human Amniotic Fluid and Bone Marrow Mesenchymal Stem Cells October 2019 International Journal of Stem Cells **12**(3) DOI: 10.15283/ijsc18087
5. *Noort, W. A., Kruisselbrink, A. B., in't Anker, P. S., Kruger, M., van Bezooijen, R. L., de Paus, R. A., Heemskerk, M. H. M., Löwik, C. W. G. M., Falkenburg, J. H., Willemze, R., & Fibbe, W. E.* (2002). Mesenchymal stem cells promote engraftment of human umbilical cord blood-derived CD34(+) cells in NOD/SCID mice. Experimental Hematology, **30**(8), 870–878. DOI: 10.1016/s0301-472x(02)00820-2
6. *Friedenstein, A. J., Chailakhyan, R. K., & Gerasimov, U. V.* (1987). Bone marrow osteogenic stem cells: In vitro cultivation and transplantation in diffusion chambers. Cell and Tissue Kinetics, **20**(3), 263–272. DOI: 10.1111/j.1365-2184.1987.tb01309.x
7. *Friedenstein, A. J., Gorskaja, J. F., & Kulagina, N. N.* (1976). Fibroblast precursors in normal and irradiated mouse hematopoietic organs. Experimental Hematology, **4**(5), 267–274.
8. *Bianco, P., Costantini, M., Dearden, L. C., & Bonucci, E.* (1988). Alkaline phosphatase positive precursors of adipocytes in the human bone marrow. British Journal of Haematology, **68**(4), 401–403. DOI: 10.1111/j.1365-2141.1988.tb04225.x
9. *Kopen, G. C., Prockop, D. J., & Phinney, D. G.* (1999). Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. Proceedings of the National Academy of Sciences of the United States of America, **96**(19), 10711–10716.
10. *Makino, S., Fukuda, K., Miyoshi, S., Konishi, F., Kodama, H., Pan, J., Sano, M., Takahashi, T., Hori, S., Abe, H., Hata, J., Umezawa, A., & Ogawa, S.* (1999). Cardiomyocytes can be generated from marrow stromal cells in vitro. The Journal of Clinical Investigation, **103**(5), 697–705. DOI: 10.1172/JCI5298
11. *Weiss, L.* (1981). Haemopoiesis in mammalian bone marrow. Ciba Foundation Symposium, **84**, 5–21. DOI: 10.1002/9780470720660.ch2
12. *van Servellen, A., & Oba, I.* (2014). Stem cell research: Trends in and perspectives on the evolving international landscape. Research Trends. Elsevier.
13. *Krugljakov, P. V., Pohmatova, E., Klimovich, V. B., & Zarickij, A. Ju.* (2006). Mezenhimnye stvolovye kletki i immunopatologicheskie sostojanija organizma. Geny i kletki, 1(3).
14. *Zhao, R. C., Liao, L., & Han, Q.* (2004). Mechanisms of and perspectives on the mesenchymal stem cell in immunotherapy. The Journal of Laboratory and Clinical Medicine, *143*(5), 284–291. DOI: 10.1016/j.lab.2003.11.009
15. *Jorgensen, C., Djouad, F., Apparailly, F., & Noël, D.* (2003). Engineering mesenchymal stem cells for immunotherapy. Gene Therapy, **10**(10), 928–931. DOI: 10.1038/sj.gt.3302019
16. *Cheng, L., Hammond, H., Ye, Z., Zhan, X., & Dravid, G. (*2003). Human adult marrow cells support prolonged expansion of human embryonic stem cells in culture. Stem Cells (Dayton, Ohio), **21**(2), 131–142. DOI: 10.1634/stemcells.21-2-131
17. *Aqmasheh, S., Shamsasanjan, K., Akbarzadehlaleh, P., Pashoutan Sarvar, D., & Timari, H.* (2017). Effects of Mesenchymal Stem Cell Derivatives on Hematopoiesis and Hematopoietic Stem Cells. Advanced Pharmaceutical Bulletin, 7(2), 165–177. DOI: 10.15171/apb.2017.021
18. *Boquest, A. C., Shahdadfar, A., Brinchmann, J. E., & Collas, P.* (2006). Isolation of stromal stem cells from human adipose tissue. Methods in Molecular Biology (Clifton, N.J.), **325**, 35–46. DOI: 10.1385/1-59745-005-7:35
19. *Zachar, V., Rasmussen, J. G., & Fink, T.* (2011). Isolation and growth of adipose tissue-derived stem cells. Methods in Molecular Biology (Clifton, N.J.), **698**, 37–49. DOI: 10.1007/978-1-60761-999-4_4
20. *Matsumoto, D., Shigeura, T., Sato, K., Inoue, K., Suga, H., Kato, H., Aoi, N., Murase, S., Gonda, K., & Yoshimura, K.* (2007). Influences of preservation at various temperatures on liposuction aspirates. Plastic and Reconstructive Surgery, **120**(6), 1510–1517. DOI: 10.1097/01.prs.0000288015.70922.e4
21. *Koç, O. N., Gerson, S. L., Cooper, B. W., Dyhouse, S. M., Haynesworth, S. E., Caplan, A. I., & Lazarus, H. M.* (2000). Rapid hematopoietic recovery after coinfusion of autologous-blood stem cells and culture-expanded marrow mesenchymal stem cells in advanced breast cancer patients receiving high-dose chemotherapy. Journal of Clinical Oncology, **18**(2), 307-307.
22. *Lindroos, B., Suuronen, R., & Miettinen, S.* (2011). The potential of adipose stem cells in regenerative medicine. Stem Cell Reviews and Reports, **7**(2), 269–291. DOI: 10.1007/s12015-010-9193-7
23. *Terskih, V. V., & Kiseljova, E. V.* (2010). Biologicheskie osobennosti i terapevticheskij potencial stromal'nyh kletok zhirovoj tkani. Obzor. Plasticheskaja Hirurgija i Kosmetologija, **4**, 613–622.
24. *Oedayrajsingh-Varma, M. J., van Ham, S. M., Knippenberg, M., Helder, M. N., Klein-Nulend, J., Schouten, T. E., Ritt, M. J. P. F., & van Milligen, F. J.* (2006). Adipose tissue-derived mesenchymal stem cell yield and growth characteristics are affected by the tissue-harvesting procedure. Cytotherapy, **8**(2), 166–177. DOI: 10.1080/14653240600621125
25. *Poznanski, W. J., Waheed, I., & Van, R.* (1973). Human fat cell precursors. Morphologic and metabolic differentiation in culture. Laboratory Investigation; a Journal of Technical Methods and Pathology, **29**(5), 570–576.
26. *Brown, S. A., Levi, B., Lequeux, C., Lequex, C., Wong, V. W., Mojallal, A., & Longaker, M. T.* (2010). Basic science review on adipose tissue for clinicians. Plastic and Reconstructive Surgery, **126**(6), 1936–1946. DOI: 10.1097/PRS.0b013e3181f44790
27. *Zuk, P. A., Zhu, M., Mizuno, H., Huang, J., Futrell, J. W., Katz, A. J., Benhaim, P., Lorenz, H. P., & Hedrick, M. H.* (2001). Multilineage cells from human adipose tissue: Implications for cell-based therapies. Tissue Engineering, **7**(2), 211–228. DOI: 10.1089/107632701300062859
28. *Dubois, S. G., Floyd, E. Z., Zvonic, S., Kilroy, G., Wu, X., Carling, S., Halvorsen, Y. D. C., Ravussin, E., & Gimble, J. M.* (2008). Isolation of human adipose-derived stem cells from biopsies and liposuction specimens. Methods in Molecular Biology (Clifton, N.J.), **449**, 69–79. DOI: 10.1007/978-1-60327-169-1_5
29. *Eom, Y. W., Lee, J. E., Yang, M. S., Jang, I. K., Kim, H. E., Lee, D. H., Kim, Y. J., Park, W. J., Kong, J. H., Shim, K. Y., Lee, J. I., & Kim, H. S.* (2011). Rapid isolation of adipose tissue-derived stem cells by the storage of lipoaspirates. Yonsei Medical Journal, **52**(6), 999–1007. DOI: 10.3349/ymj.2011.52.6.999
30. *Gimble, J. M., Guilak, F., & Bunnell, B. A.* (2010). Clinical and preclinical translation of cell-based therapies using adipose tissue-derived cells. Stem Cell Research & Therapy, **1**(2), 19. DOI: 10.1186/scrt19
31. *Gir, P., Oni, G., Brown, S. A., Mojallal, A., & Rohrich, R. J.* (2012). Human adipose stem cells: Current clinical applications. Plastic and Reconstructive Surgery, **129**(6), 1277–1290. DOI: 10.1097/PRS.0b013e31824ecae6
32. *Lin, G., Garcia, M., Ning, H., Banie, L., Guo, Y.-L., Lue, T. F., & Lin, C.-S.* (2008). Defining stem and progenitor cells within adipose tissue. Stem Cells and Development, **17**(6), 1053–1063. DOI: 10.1089/scd.2008.0117
33. *Lin, K., Matsubara, Y., Masuda, Y., Togashi, K., Ohno, T., Tamura, T., Toyoshima, Y., Sugimachi, K., Toyoda, M., Marc, H., & Douglas, A.* (2008). Characterization of adipose tissue-derived cells isolated with the CelutionTM system. Cytotherapy, **10**(4), 417–426. DOI: 10.1080/14653240801982979
34. *Schreml, S., Babilas, P., Fruth, S., Orsó, E., Schmitz, G., Mueller, M. B., Nerlich, M., & Prantl, L.* (2009). Harvesting human adipose tissue-derived adult stem cells: Resection versus liposuction. Cytotherapy, **11**(7), 947–957. DOI: 10.3109/14653240903204322

35. *Ahmad, J., Eaves, F. F., Rohrich, R. J., & Kenkel, J. M.* (2011). The American Society for Aesthetic Plastic Surgery (ASAPS) survey: Current trends in liposuction. Aesthetic Surgery Journal, **31**(2), 214–224. DOI: 10.1177/1090820X10395508
36. *Tierney, E. P., Kouba, D. J., & Hanke, C. W.* (2011). Safety of tumescent and laser-assisted liposuction: Review of the literature. Journal of Drugs in Dermatology: JDD, **10**(12), 1363–1369.
37. *Mojallal, A., Auxenfans, C., Lequeux, C., Braye, F., & Damour, O.* (2008). Influence of negative pressure when harvesting adipose tissue on cell yield of the stromal-vascular fraction. Bio-Medical Materials and Engineering, **18**(4–5), 193–197.
38. *Kakudo, N., Tanaka, Y., Morimoto, N., Ogawa, T., Kushida, S., Hara, T., & Kusumoto, K.* (2013). Adipose-derived regenerative cell (ADRC)-enriched fat grafting: Optimal cell concentration and effects on grafted fat characteristics. Journal of Translational Medicine, **11**, 254. DOI: 10.1186/1479-5876-11-254
39. *Mizuno, H., Tobita, M., & Uysal, A. C.* (2012). Concise review: Adipose-derived stem cells as a novel tool for future regenerative medicine. Stem Cells (Dayton, Ohio), **30**(5), 804–810. DOI: 10.1002/stem.1076
40. *Shah, F. S., Wu, X., Dietrich, M., Rood, J., & Gimble, J. M.* (2013). A non-enzymatic method for isolating human adipose tissue-derived stromal stem cells. Cytotherapy, **15**(8), 979–985. DOI: 10.1016/j.jcyt.2013.04.001
41. *Francis, M. P., Sachs, P. C., Elmore, L. W., & Holt, S. E.* (2010). Isolating adipose-derived mesenchymal stem cells from lipoaspirate blood and saline fraction. Organogenesis, **6**(1), 11–14. DOI: 10.4161/org.6.1.10019
42. *Bunnell, B. A., Flaat, M., Gagliardi, C., Patel, B., & Ripoll, C.* (2008). Adipose-derived stem cells: Isolation, expansion and differentiation. Methods (San Diego, Calif.), **45**(2), 115–120. DOI: 10.1016/j.ymeth.2008.03.006
43. *Aronowitz, J. A., & Ellenhorn, J. D.* (2013). Adipose stromal vascular fraction isolation: a head-to-head comparison of four commercial cell separation systems. Plastic and Reconstructive Surgery, **132**(6), 932e-939e.
44. *Bianchi, F., Maioli, M., Leonardi, E., Olivi, E., Pasquinelli, G., Valente, S., ... & Ventura, C.* (2013). A new nonenzymatic method and device to obtain a fat tissue derivative highly enriched in pericyte-like elements by mild mechanical forces from human lipoaspirates. Cell transplantation, **22**(11), 2063-2077.
45. *Sterodimas, A., de Faria, J., Nicaretta, B., & Boriani, F.* (2011). Autologous fat transplantation versus adipose-derived stem cell-enriched lipografts: A study. Aesthetic Surgery Journal, **31**(6), 682–693. DOI: 10.1177/1090820X11415976
46. *Lin, P. P., Wang, Y., & Lozano, G.* (2010, October 5). Mesenchymal Stem Cells and the Origin of Ewing's Sarcoma [Review Article]. Sarcoma; Hindawi, ID 276463. DOI: 10.1155/2011/276463
47. *Uccelli, A., Moretta, L., & Pistoia, V.* (2008). Mesenchymal stem cells in health and disease. Nature Reviews. Immunology, **8**(9), 726–736. DOI: 10.1038/nri2395
48. *Karnoub, A. E., Dash, A. B., Vo, A. P., Sullivan, A., Brooks, M. W., Bell, G. W., Richardson, A. L., Polyak, K., Tubo, R., & Weinberg, R. A.* (2007). Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. Nature, **449**(7162), 557–563. DOI: 10.1038/nature06188
49. *Weis, S. M., & Cheresh, D. A.* (2011). Tumor angiogenesis: Molecular pathways and therapeutic targets. Nature Medicine, **17**(11), 1359–1370. DOI: 10.1038/nm.2537
50. *Li, W., Ren, G., Huang, Y., Su, J., Han, Y., Li, J., Chen, X., Cao, K., Chen, Q., Shou, P., Zhang, L., Yuan, Z.-R., Roberts, A. I., Shi, S., Le, A. D., & Shi, Y.* (2012). Mesenchymal stem cells: A double-edged sword in regulating immune responses. Cell Death and Differentiation, **19**(9), 1505–1513. DOI: 10.1038/cdd.2012.26
51. *Lalu, M. M., McIntyre, L., Pugliese, C., Fergusson, D., Winston, B. W., Marshall, J. C., Granton, J., Stewart, D. J., & Canadian Critical Care Trials Group.* (2012). Safety of cell therapy with mesenchymal stromal cells (SafeCell): A systematic review and meta-analysis of clinical trials. PloS One, **7**(10), e47559. DOI: 10.1371/journal.pone.0047559
52. *Zegers-Hochschild, F., Adamson, G. D., de Mouzon, J., Ishihara, O., Mansour, R., Nygren, K., ... & Van der Poel, S.* (2009). The international committee for monitoring assisted reproductive technology (ICMART) and the world health organization (WHO) revised glossary on ART terminology, 2009. Human reproduction, **24**(11), 2683-2687.
53. *Esteves, S. C., Sharma, R. K., Gosálvez, J., & Agarwal, A.* (2014). A translational medicine appraisal of specialized andrology testing in unexplained male infertility. International Urology and Nephrology, **46**(6), 1037–1052. DOI: 10.1007/s11255-014-0715-0
54. *Gamidov, S. I., Popova, A. Ju., & Ovchinnikov, R. I.* (2015). Neobstruktivnaja azoospermija-klinicheskie rekomendacii. RMZh, **23**(11), 595–601.
55. *Andersson, A.-M., Jørgensen, N., Frydelund-Larsen, L., Rajpert-De Meyts, E., & Skakkebaek, N. E.* (2004). Impaired Leydig cell function in infertile men: A study of 357 idiopathic infertile men and 318 proven fertile controls. The Journal of Clinical Endocrinology and Metabolism, **89**(7), 3161–3167. DOI: 10.1210/jc.2003-031786
56. *Bhasin, S., de Kretser, D. M., & Baker, H. W.* (1994). Clinical review 64: Pathophysiology and natural history of male infertility. The Journal of Clinical Endocrinology and Metabolism, **79**(6), 1525–1529. DOI: 10.1210/jcem.79.6.7989450
57. *Boivin, J., Bunting, L., Collins, J. A., & Nygren, K. G.* (2007). International estimates of infertility prevalence and treatment-seeking: Potential need and demand for infertility medical care. Human Reproduction (Oxford, England), **22**(6), 1506–1512. DOI: 10.1093/humrep/dem046
58. *Hull, M. G., Glazener, C. M., Kelly, N. J., Conway, D. I., Foster, P. A., Hinton, R. A., Coulson, C., Lambert, P. A., Watt, E. M., & Desai, K. M.* (1985). Population study of causes, treatment, and outcome of infertility. British Medical Journal (Clinical Research Ed.), **291**(6510), 1693–1697.
59. *Saunders, D. M., Mathews, M., & Lancaster, P. A.* (1988). The Australian Register: Current research and future role. A preliminary report. Annals of the New York Academy of Sciences, **541**, 7–21. DOI: 10.1111/j.1749-6632.1988.tb22237.x
60. *Tan, S. L., Doyle, P., Campbell, S., Beral, V., Rizk, B., Brinsden, P., Mason, B., & Edwards, R. G.* (1992). Obstetric outcome of in vitro fertilization pregnancies compared with normally conceived pregnancies. American Journal of Obstetrics and Gynecology, **167**(3), 778–784. DOI: 10.1016/s0002-9378(11)91589-0
61. Goldenberg, R. L., Culhane, J. F., Iams, J. D., & Romero, R. (2008). Epidemiology and causes of preterm birth. Lancet (London, England), 371(9606), 75–84. DOI: 10.1016/S0140-6736(08)60074-4
62. *Matzuk, M. M., & Lamb, D. J.* (2008). The biology of infertility: Research advances and clinical challenges. Nature Medicine, **14**(11), 1197–1213. DOI: 10.1038/nm.f.1895
63. *Kurilo, L. F., Andreeva, M. V., Kolomiec, O. V., Sorokina, T. M., Chernyh, V. B., Shilejko, L. V., Hajat, S. Sh., Demikova, N. S., & Kozlova, S. I.* (2014, November 29). Geneticheskie sindromy s narushenijami razvitija organov polovoj sistemy (Text.Serial.Journal No. 4). Andrologija i genital'naja hirurgija. DOI: 10.17650/2070-9781-2013-4-17-27
64. *Brandes, M., Hamilton, C. J. C. M., de Bruin, J. P., Nelen, W. L. D. M., & Kremer, J. A. M.* (2010). The relative contribution of IVF to the total ongoing pregnancy rate in a subfertile cohort. Human Reproduction, **25**(1), 118–126. DOI: 10.1093/humrep/dep341
65. *Hamada, A., Esteves, S. C., Nizza, M., & Agarwal, A.* (2012). Unexplained male infertility: Diagnosis and management. International Braz J Urol: Official Journal of the Brazilian Society of Urology, **38**(5), 576–594. DOI: 10.1590/s1677-55382012000500002
66. *Zini, A., Bielecki, R., Phang, D., & Zenzes, M. T.* (2001). Correlations between two markers of sperm DNA integrity, DNA denaturation and DNA fragmentation, in fertile and infertile men. Fertility and Sterility, **75**(4), 674–677. DOI: 10.1016/s0015-0282(00)01796-9
67. *Lewis, S. E. M.* (2015). Should sperm DNA fragmentation testing be included in the male infertility work-up? Reproductive BioMedicine Online, **31**(2), 134–137. DOI: 10.1016/j.rbmo.2015.05.006
68. *Schoor, R. A., Elhanbly, S., Niederberger, C. S., & Ross, L. S.* (2002). The role of testicular biopsy in the modern management of male infertility. The Journal of Urology, **167**(1), 197–200.
69. *Esteves, S. C., Prudencio, C., Seol, B., Verza, S., Knoedler, C., & Agarwal, A.* (2014). Comparison of sperm retrieval and reproductive outcome in azoospermic men with testicular failure and obstructive azoospermia treated for infertility. Asian Journal of Andrology, **16**(4), 602–606. DOI: 10.4103/1008-682X.126015
70. *Baker, K., & Sabanegh, E.* (2013). Obstructive azoospermia: Reconstructive techniques and results. Clinics, **68**(Suppl 1), 61–73. DOI: 10.6061/clinics/2013(Sup01)07
71. *Esteves, S. C.* (2015). Clinical management of infertile men with nonobstructive azoospermia. Asian Journal of Andrology, **17**(3), 459–470. DOI: 10.4103/1008-682X.148719
72. *Esteves, S. C., Miyaoka, R., & Agarwal, A.* (2011a). An update on the clinical assessment of the infertile male. [Corrected]. Clinics (Sao Paulo, Brazil), **66**(4), 691–700. DOI: 10.1590/s1807-59322011000400026
73. *Carpi, A., Sabanegh, E., & Mechanick, J.* (2009). Controversies in the management of nonobstructive azoospermia. Fertility and Sterility, **91**(4), 963–970. DOI: 10.1016/j.fertnstert.2009.01.083
74. *Cocuzza, M., Alvarenga, C., & Pagani, R.* (2013). The epidemiology and etiology of azoospermia. Clinics, **68**(Suppl 1), 15–26. DOI: 10.6061/clinics/2013(Sup01)03
75. Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society for Male Reproduction and Urology. (2018). Evaluation of the azoospermic male: A committee opinion. Fertility and Sterility, **109**(5), 777–782. DOI: 10.1016/j.fertnstert.2018.01.043
76. *Gudeloglu, A., & Parekattil, S. J.* (2013). Update in the evaluation of the azoospermic male. Clinics, **68**(Suppl 1), 27–34. DOI: 10.6061/clinics/2013(Sup01)04
77. *Hung, A. J., King, P., & Schlegel, P. N.* (2007). Uniform testicular maturation arrest: A unique subset of men with nonobstructive azoospermia. The Journal of Urology, **178**(2), 608–612; discussion 612. DOI: 10.1016/j.juro.2007.03.125
78. *Sussman, E. M., Chudnovsky, A., & Niederberger, C. S.* (2008). Hormonal evaluation of the infertile male: Has it evolved? The Urologic Clinics of North America, **35**(2), 147–155, vii. DOI: 10.1016/j.ucl.2008.01.010
79. *Bobjer, J., Naumovska, M., Giwercman, Y. L., & Giwercman, A.* (2012).

High prevalence of androgen deficiency and abnormal lipid profile in infertile men with non-obstructive azoospermia. International Journal of Andrology, **35**(5), 688–694. DOI: 10.1111/j.1365-2605.2012.01277.x
80. *Reifsnyder, J. E., Ramasamy, R., Husseini, J., & Schlegel, P. N.* (2012). Role of optimizing testosterone before microdissection testicular sperm extraction in men with nonobstructive azoospermia. The Journal of Urology, **188**(2), 532–536. DOI: 10.1016/j.juro.2012.04.002
81. *Kumar, R.* (2013). Medical management of non-obstructive azoospermia. Clinics, **68**(Suppl 1), 75–79. DOI: 10.6061/clinics/2013(Sup01)08
82. *Hammoud, A., Carrell, D. T., Meikle, A. W., Xin, Y., Hunt, S. C., Adams, T. D., & Gibson, M.* (2010). An aromatase polymorphism modulates the relationship between weight and estradiol levels in obese men. Fertility and Sterility, **94**(5), 1734–1738. DOI: 10.1016/j.fertnstert.2009.10.037
83. *Isidori, A. M., Caprio, M., Strollo, F., Moretti, C., Frajese, G., Isidori, A., & Fabbri, A.* (1999). Leptin and androgens in male obesity: Evidence for leptin contribution to reduced androgen levels. The Journal of Clinical Endocrinology and Metabolism, **84**(10), 3673–3680. DOI: 10.1210/jcem.84.10.6082
84. *Strain, G., Zumoff, B., Rosner, W., & Pi-Sunyer, X.* (1994). The relationship between serum levels of insulin and sex hormone-binding globulin in men: The effect of weight loss. The Journal of Clinical Endocrinology and Metabolism, **79**(4), 1173–1176. DOI: 10.1210/jcem.79.4.7962291
85. *Chiba, K., Enatsu, N., & Fujisawa, M.* (2016). Management of non-obstructive azoospermia. Reproductive Medicine and Biology, **15**(3), 165–173. DOI: 10.1007/s12522-016-0234-z
86. *Silber, S. J.* (2000). Microsurgical TESE and the distribution of spermatogenesis in non-obstructive azoospermia. Human Reproduction (Oxford, England), **15**(11), 2278–2284. DOI: 10.1093/humrep/15.11.2278
87. *Esteves, S. C., Miyaoka, R., & Agarwal, A.* (2011b). Sperm retrieval techniques for assisted reproduction. International Braz J Urol: Official Journal of the Brazilian Society of Urology, **37**(5), 570–583. DOI: 10.1590/s1677-55382011000500002
88. *Hendriks, S., Dancet, E. a. F., Meissner, A., van der Veen, F., Mochtar, M. H., & Repping, S.* (2014). Perspectives of infertile men on future stem cell treatments for nonobstructive azoospermia. Reproductive Biomedicine Online, **28**(5), 650–657. DOI: 10.1016/j.rbmo.2014.01.011
89. *Palermo, G., Joris, H., Devroey, P., & Van Steirteghem, A. C.* (1992). Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet (London, England), **340**(8810), 17–18. DOI: 10.1016/0140-6736(92)92425-f
90. *Belva, F., De Schrijver, F., Tournaye, H., Liebaers, I., Devroey, P., Haentjens, P., & Bonduelle, M.* (2011). Neonatal outcome of 724 children born after ICSI using non-ejaculated sperm. Human Reproduction (Oxford, England), **26**(7), 1752–1758. DOI: 10.1093/humrep/der121
91. *Ivell, R., Kotula-Balak, M., Glynn, D., Heng, K., & Anand-Ivell, R.* (2011). Relaxin family peptides in the male reproductive system—A critical appraisal. Molecular Human Reproduction, **17**(2), 71–84. DOI: 10.1093/molehr/gaq086
92. *Schlegel, P. N.* (2009). Evaluation of male infertility. Minerva ginecologica, **61**(4), 261.
93. Cyranoski, D. (2013). Stem cells boom in vet clinics. Nature, 496(7444), 148–149. DOI: 10.1038/496148a
94. *Fazeli, Z., Abedindo, A., Omrani, M. D., & Ghaderian, S. M. H.* (2018). Mesenchymal Stem Cells (MSCs) Therapy for Recovery of Fertility: A Systematic Review. Stem Cell Reviews and Reports, **14**(1), 1–12. DOI: 10.1007/s12015-017-9765-x
95. *Hosseinzadeh Shirzeily, M., Pasbakhsh, P., Amidi, F., Mehrannia, K., & Sobhani, A.* (2013). Comparison of differentiation potential of male mouse adipose tissue and bone marrow derived-mesenchymal stem cells into germ cells. Iranian Journal of Reproductive Medicine, **11**(12), 965–976.
96. *Nayernia, K., Lee, J. H., Drusenheimer, N., Nolte, J., Wulf, G., Dressel, R., Gromoll, J., & Engel, W.* (2006). Derivation of male germ cells from bone marrow stem cells. Laboratory Investigation; a Journal of Technical Methods and Pathology, **86**(7), 654–663. DOI: 10.1038/labinvest.3700429
97. *Nayernia, K., Nolte, J., Michelmann, H. W., Lee, J. H., Rathsack, K., Drusenheimer, N., Dev, A., Wulf, G., Ehrmann, I. E., Elliott, D. J., Okpanyi, V., Zechner, U., Haaf, T., Meinhardt, A., & Engel, W.* (2006). In vitro-differentiated embryonic stem cells give rise to male gametes that can generate offspring mice. Developmental Cell, **11**(1), 125–132. DOI: 10.1016/j.devcel.2006.05.010
98. *Yazawa, T., Mizutani, T., Yamada, K., Kawata, H., Sekiguchi, T., Yoshino, M., Kajitani, T., Shou, Z., Umezawa, A., & Miyamoto, K.* (2006). Differentiation of adult stem cells derived from bone marrow stroma into Leydig or adrenocortical cells. Endocrinology, **147**(9), 4104–4111. DOI: 10.1210/en.2006-0162
99. *Hua, J., Yu, H., Dong, W., Yang, C., Gao, Z., Lei, A., Sun, Y., Pan, S., Wu, Y., & Dou, Z.* (2009). Characterization of mesenchymal stem cells (MSCs) from human fetal lung: Potential differentiation of germ cells. Tissue and Cell, **41**(6), 448–455. DOI: 10.1016/j.tice.2009.05.004
100. *Shlush, E., Maghen, L., Swanson, S., Kenigsberg, S., Moskovtsev, S., Barretto, T., Gauthier-Fisher, A., & Librach, C. L.* (2017). In vitro generation of Sertoli-like and haploid spermatid-like cells from human umbilical cord perivascular cells. Stem Cell Research & Therapy, **8**(1), 37. DOI: 10.1186/s13287-017-0491-8
101. *Asgari, H. R., Akbari, M., Abbasi, M., Ai, J., Korouji, M., Aliakbari, F., Babatunde, K. A., Aval, F. S., & Joghataei, M. T.* (2015). Human Wharton's jelly-derived mesenchymal stem cells express oocyte developmental genes during co-culture with placental cells. Iranian Journal of Basic Medical Sciences, **18**(1), 22–29.
102. *Xie, L., Lin, L., Tang, Q., Li, W., Huang, T., Huo, X., Liu, X., Jiang, J., He, G., & Ma, L.* (2015). Sertoli cell-mediated differentiation of male germ cell-like cells from human umbilical cord Wharton's jelly-derived mesenchymal stem cells in an in vitro co-culture system. European Journal of Medical Research, **20**, 9. DOI: 10.1186/s40001-014-0080-6
103. *Sabbaghi, M. A., Bahrami, A. R., Feizzade, B., Kalantar, S. M., Matin, M. M., Kalantari, M., Aflatoonian, A., & Saeinasab, M.* (2012). Trial evaluation of bone marrow derived mesenchymal stem cells (MSCs) transplantation in revival of spermatogenesis in testicular torsion. Middle East Fertility Society Journal, **17**(4), 243–249. DOI: 10.1016/j.mefs.2012.06.001
104. *Rahmanifar, F., Tamadon, A., Mehrabani, D., Zare, S., Abasi, S., Keshavarz, S., Dianatpour, M., Khodabandeh, Z., Jahromi, I. R. G., & Koohi-Hoseinabadi, O.* (2016). Histomorphometric evaluation of treatment of rat azoosper-mic seminiferous tubules by allotransplantation of bone marrow-derived mesenchymal stem cells. Iranian Journal of Basic Medical Sciences, **19**(6), 653–661.
105. *Vahdati, A., Fathi, A., Hajihoseini, M., Aliborzi, G., & Hosseini, E.* (2017). The Regenerative Effect of Bone Marrow-Derived Stem Cells in Spermatogenesis of Infertile Hamster. World Journal of Plastic Surgery, **6**(1), 18–25.
106. *Cakici, C., Buyrukcu, B., Duruksu, G., Haliloglu, A. H., Aksoy, A., Isık, A., Uludag, O., Ustun, H., Subası, C., & Karaoz, E.* (2013, February 18). Recovery of Fertility in Azoospermia Rats after Injection of Adipose-Tissue-Derived Mesenchymal Stem Cells: The Sperm Generation [Research Article]. BioMed Research International; Hindawi. DOI: 10.1155/2013/529589
107. *Zhang, D., Liu, X., Peng, J., He, D., Lin, T., Zhu, J., Li, X., Zhang, Y., & Wei, G.* (2014). Potential Spermatogenesis Recovery with Bone Marrow Mesenchymal Stem Cells in an Azoospermic Rat Model. International Journal of Molecular Sciences, **15**(8), 13151–13165. DOI: 10.3390/ijms150813151
108. *Aghamir, S. M. K., Salavati, A., Yousefie, R., Tootian, Z., Ghazaleh, N., Jamali, M., & Azimi, P.* (2014). Does Bone Marrow–derived Mesenchymal Stem Cell Transfusion Prevent Antisperm Antibody Production After Traumatic Testis Rupture? Urology, **84**(1), 82–86. DOI: 10.1016/j.urology.2014.03.009
109. *Hsiao, C.-H., Ji, A. T.-Q., Chang, C.-C., Cheng, C.-J., Lee, L.-M., & Ho, J. H.-C.* (2015). Local injection of mesenchymal stem cells protects testicular torsion-induced germ cell injury. Stem Cell Research & Therapy, **6**(1). DOI: 10.1186/s13287-015-0079-0
110. *Ghasemzadeh-Hasankolaei, M., Batavani, R., Eslaminejad, M. B., & Sayahpour, F.* (2016). Transplantation of Autologous Bone Marrow Mesenchymal Stem Cells into the Testes of Infertile Male Rats and New Germ Cell Formation. International Journal of Stem Cells, **9**(2), 250–263. DOI: 10.15283/ijsc16010
111. *Abd Allah, S. H., Pasha, H. F., Abdelrahman, A. A., & Mazen, N. F.* (2017). Molecular effect of human umbilical cord blood CD34-positive and CD34-negative stem cells and their conjugate in azoospermic mice. Molecular and Cellular Biochemistry, **428**(1–2), 179–191. DOI: 10.1007/s11010-016-2928-2
112. *Yang, R. F., Liu, T. H., Zhao, K., & Xiong, C. L.* (2014). Enhancement of mouse germ cell-associated genes expression by injection of human umbilical cord mesenchymal stem cells into the testis of chemical-induced azoospermic mice. Asian Journal of Andrology, **16**(5), 698.
113. *Hajihoseini, M., Vahdati, A., Hosseini, S. E., Mehrabani, D., & Tamadon, A.* (2017). Induction of spermatogenesis after stem cell therapy of azoospermic guinea pigs. DOI: 10.24099/VET.ARHIV.151209
114. *Liu, H., Chen, M., Liu, L., Ren, S., Cheng, P., & Zhang, H.* (2018). Induction of Human Adipose-Derived Mesenchymal Stem Cells into Germ Lineage Using Retinoic Acid. Cellular Reprogramming, **20**(2), 127–134. DOI: 10.1089/cell.2017.0063
115. *Sherif, I. O., Sabry, D., Abdel-Aziz, A., & Sarhan, O. M.* (2018). The role of mesenchymal stem cells in chemotherapy-induced gonadotoxicity. Stem Cell Research & Therapy, **9**(1), 196. DOI: 10.1186/s13287-018-0946-6
116. *Leatherman, J.* (2013). Stem cells supporting other stem cells. Frontiers in Genetics, 4. DOI: 10.3389/fgene.2013.00257
117. *Mansour, A., Abou-Ezzi, G., Sitnicka, E., Jacobsen, S. E. W., Wakkach, A., & Blin-Wakkach, C.* (2012). Osteoclasts promote the formation of hematopoietic stem cell niches in the bone marrow. The Journal of Experimental Medicine, **209**(3), 537–549. DOI: 10.1084/jem.20110994
118. *Mital, P., Kaur, G., & Dufour, J. M.* (2010). Immunoprotective sertoli cells: Making allogeneic and xenogeneic transplantation feasible. Reproduction (Cambridge, England), **139**(3), 495–504. DOI: 10.1530/REP-09-0384
119. *AlZoubi, A. M.* (2014). Abstract 3038: Intra-testicular transplantation of purified autologous stem cells for treatment of chemotherapy-induced male infertility. Cancer Research, **74**(19 Supplement), 3038–3038. DOI: 10.1158/1538-7445.AM2014-3038
120. *Knigavko, O., & Bezborodova, I.* (2017). 215 Using Autological Stem Cells for Treatment of Not Obstractive Azoospermia. The Journal of Sexual Medicine, **14**(1), S60. DOI: 10.1016/j.jsxm.2016.11.131

121. *Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F., Krause, D., Deans, R., Keating, A., Prockop, D., & Horwitz, E.* (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy, **8**(4), 315–317. DOI: 10.1080/14653240600855905
122. *Gronthos, Stan, Zannettino, A. C. W., Hay, S. J., Shi, S., Graves, S. E., Kortesidis, A., & Simmons, P. J.* (2003). Molecular and cellular characterisation of highly purified stromal stem cells derived from human bone marrow. Journal of Cell Science, **116**(Pt 9), 1827–1835. DOI: 10.1242/jcs.00369
123. *Ohgushi, H., Kotobuki, N., Funaoka, H., Machida, H., Hirose, M., Tanaka, Y., & Takakura, Y.* (2005). Tissue engineered ceramic artificial joint—Ex vivo osteogenic differentiation of patient mesenchymal cells on total ankle joints for treatment of osteoarthritis. Biomaterials, **26**(22), 4654–4661. DOI: 10.1016/j.biomaterials.2004.11.055
124. *Wongchuensoontorn, C., Liebehenschel, N., Schwarz, U., Schmelzeisen, R., Gutwald, R., Ellis, E., & Sauerbier, S.* (2009). Application of a new chair-side method for the harvest of mesenchymal stem cells in a patient with nonunion of a fracture of the atrophic mandible—A case report. Journal of Cranio-Maxillo-Facial Surgery: Official Publication of the European Association for Cranio-Maxillo-Facial Surgery, **37**(3), 155–161. DOI: 10.1016/j.jcms.2008.11.002
125. *Gronthos, S., Franklin, D. M., Leddy, H. A., Robey, P. G., Storms, R. W., & Gimble, J. M.* (2001). Surface protein characterization of human adipose tissue-derived stromal cells. Journal of Cellular Physiology, **189**(1), 54–63. DOI: 10.1002/jcp.1138
126. *Tsai, M.-S., Lee, J.-L., Chang, Y.-J., & Hwang, S.-M.* (2004). Isolation of human multipotent mesenchymal stem cells from second-trimester amniotic fluid using a novel two-stage culture protocol. Human Reproduction (Oxford, England), *19*(6), 1450–1456. DOI: 10.1093/humrep/deh279
127. *Zvaifler, N. J., Marinova-Mutafchieva, L., Adams, G., Edwards, C. J., Moss, J., Burger, J. A., & Maini, R. N.* (2000). Mesenchymal precursor cells in the blood of normal individuals. Arthritis Research, **2**(6), 477–488. DOI: 10.1186/ar130
128. *Igura, K., Zhang, X., Takahashi, K., Mitsuru, A., Yamaguchi, S., & Takahashi, T. A.* (2004). Isolation and characterization of mesenchymal progenitor cells from chorionic villi of human placenta. Cytotherapy, **6**(6), 543-553.
129. *Zuk, P. A., Zhu, M., Ashjian, P., De Ugarte, D. A., Huang, J. I., Mizuno, H., ... & Hedrick, M. H.* (2002). Human adipose tissue is a source of multipotent stem cells. Molecular biology of the cell, **13**(12), 4279-4295.
130. *Miura, M., Gronthos, S., Zhao, M., Lu, B., Fisher, L. W., Robey, P. G., & Shi, S.* (2003). SHED: stem cells from human exfoliated deciduous teeth. Proceedings of the National Academy of Sciences, **100**(10), 5807-5812.
131. Parte, S., Bhartiya, D., Telang, J., Daithankar, V., Salvi, V., Zaveri, K., & Hinduja, I. (2011). Detection, characterization, and spontaneous differentiation in vitro of very small embryonic-like putative stem cells in adult mammalian ovary. Stem cells and development, **20**(8), 1451-1464.
132. *Iwata, T., Yamato, M., Zhang, Z., Mukobata, S., Washio, K., Ando, T., ... & Ishikawa, I.* (2010). Validation of human periodontal ligament-derived cells as a reliable source for cytotherapeutic use. Journal of Clinical Periodontology, **37**(12), 1088-1099.
133. *Hasebe, Y., Hasegawa, S., Hashimoto, N., Toyoda, M., Matsumoto, K., Umezawa, A., ... & Akamatsu, H.* (2011). Analysis of cell characterization using cell surface markers in the dermis. Journal of dermatological science, **62**(2), 98-106.
134. *Yu, G., Wu, X., Dietrich, M. A., Polk, P., Scott, L. K., Ptitsyn, A. A., & Gimble, J. M.* (2010). Yield and characterization of subcutaneous human adipose-derived stem cells by flow cytometric and adipogenic mRNA analyzes. Cytotherapy, **12**(4), 538-546.
135. *Kadar, K., Kiraly, M., Porcsalmy, B., Molnar, B., Racz, G. Z., Blazsek, J., ... & Varga, G.* (2009). Differentiation potential of stem cells from human dental origin-promise for tissue engineering. J Physiol Pharmacol, **60**(Suppl 7), 167-175.
136. *Kyurkchiev, S., Shterev, A., & Dimitrov, R.* (2010). Assessment of presence and characteristics of multipotent stromal cells in human endometrium and decidua. Reproductive biomedicine online, **20**(3), 305-313.
137. *Royer-Pokora, B., Busch, M., Beier, M., Duhme, C., de Torres, C., Mora, J., ... & Royer, H. D.* (2010). Wilms tumor cells with WT1 mutations have characteristic features of mesenchymal stem cells and express molecular markers of paraxial mesoderm. Human molecular genetics, **19**(9), 1651-1668.
138. *Mousavi Niri, N., Jaberipour, M., Razmkhah, M., Ghaderi, A., & Habibagahi, M.* (2009). Mesenchymal stem cells do not suppress lymphoblastic leukemic cell line proliferation. Iranian Journal of Immunology, **6**(4), 186-194.
139. *Orciani, M., Mariggiò, M. A., Morabito, C., Di Benedetto, G., & Di Primio, R.* (2010). Functional characterization of calcium-signaling pathways of human skin-derived mesenchymal stem cells. Skin pharmacology and physiology, **23**(3), 124-132.
140. *Bühring, H. J., Treml, S., Cerabona, F., De Zwart, P., Kanz, L., & Sobiesiak, M.* (2009). Phenotypic characterization of distinct human bone marrow–derived MSC subsets. Annals of the New York Academy of Sciences, **1176**(1), 124-134.
141. *Latif, N., Sarathchandra, P., Thomas, P. S., Antoniw, J., Batten, P., Chester, A. H., ... & Yacoub, M. H.* (2007). Characterization of structural and signaling molecules by human valve interstitial cells and comparison to human mesenchymal stem cells. JOURNAL OF HEART VALVE DISEASE, **16**(1), 56.
142. *Gronthos, S., Graves, S. E., Ohta, S., & Simmons, P. J.* (1994). The STRO-1+ fraction of adult human bone marrow contains the osteogenic precursors. DOI: 10.1182/blood.V84.12.4164.bloodjournal84124164
143. *Gronthos, S., Zannettino, A. C., Graves, S. E., Ohta, S., Hay, S. J., & Simmons, P. J.* (1999). Differential cell surface expression of the STRO-1 and alkaline phosphatase antigens on discrete developmental stages in primary cultures of human bone cells. Journal of Bone and Mineral Research, **14**(1), 47-56.
144. *Stewart, K., Walsh, S., Screen, J., Jefferiss, C. M., Chainey, J., Jordan, G. R., & Beresford, J. N.* (1999). Further characterization of cells expressing STRO-1 in cultures of adult human bone marrow stromal cells. Journal of Bone and Mineral Research, **14**(8), 1345-1356.
145**.** *Simmons, P. J., & Torok-Storb, B.* (1991). Identification of stromal cell precursors in human bone marrow by a novel monoclonal antibody, STRO-1. DOI: 10.1182/blood.V78.1.55.55
146. *Simmons, P. J., Gronthos, S., Zannettino, A., Ohta, S., & Graves, S.* (1994). Isolation, characterization and functional activity of human marrow stromal progenitors in hemopoiesis. Progress in clinical and biological research, **389**, 271.
147. *Walsh, S., Jefferiss, C., Stewart, K., Jordan, G. R., Screen, J., & Beresford, J. N.* (2000). Expression of the developmental markers STRO-1 and alkaline phosphatase in cultures of human marrow stromal cells: regulation by fibroblast growth factor (FGF)-2 and relationship to the expression of FGF receptors 1–4. Bone, **27**(2), 185-195.
148. *Conget, P. A., & Minguell, J. J.* (1999). Phenotypical and functional properties of human bone marrow mesenchymal progenitor cells. Journal of cellular physiology, **181**(1), 67-73.
149. *Pittenger, M. F., Mackay, A. M., Beck, S. C., Jaiswal, R. K., Douglas, R., Mosca, J. D., ... & Marshak, D. R.* (1999). Multilineage potential of adult human mesenchymal stem cells. science, *284*(5411), 143-147.

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ВОССТАНОВЛЕНИЕ СПЕРМАТОГЕНЕЗА У МУЖЧИН МЕЗЕНХИМАЛЬНЫМИ СТВОЛОВЫМИ КЛЕТКАМИ ЖИРОВОЙ ТКАНИ (ЛИТЕРАТУРНЫЙ ОБЗОР)

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Стволовые клетки рассматриваются как новые многообещающие терапевтические агенты при лечении мужского бесплодия из-за их высокого потенциала дифференцировки и неограниченного предложения. В этом обзоре мы обобщили современные взгляды на применение мезенхимальных стволовых клеток в репродуктивной медицине.

Ключевые слова: вспомогательные репродуктивные технологии; фактор мужского бесплодия; необструктивная азооспермия; мезенхимальные стволовые клетки; жировая ткань; костный мозг

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