

# Therapeutic effects of adipose derived mesenchymal stem cells on remyelination process in inflammatory demyelinating diseases

Nazem Ghasemi

Correspondence: [Ghasemi\\_anatomy@yahoo.com](mailto:Ghasemi_anatomy@yahoo.com)



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Department of Anatomical Sciences and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

## Abstract

Multiple sclerosis “MS” is a frequent demyelinating disease that affecting the central nervous system and associated with a progressive clinical course or severe disability in young adults. This narrative review summarizes the comprehensive information about adipose derived mesenchymal stem cells as one of the best sources for cell based therapy in demyelinating disease. The precise cause of MS is unknown, but the current evidence suggests that it can be linked to both genetic predisposition and environmental factors. During this abnormal condition, multifocal zones of inflammation due to focal immune cells infiltration and vascular abnormalities as well as change in plasmalemma permeability can occur which may be the primary cause of myelin sheath destruction. In addition to this pathological change, the formations of central nerve system plaques can also occur which crosstalk with the correct transmission of nerve impulse and finally lead to neuronal dysfunction. Conventional drug therapies for MS are not able to stop the degeneration of nerve tissue. So, stem cell based therapies has been proposed for the treatment of MS. In this narrative review, some of the characteristics and therapeutic effects of adipose-derived stem cells as a suitable cell source for cell transplantation in MS disease have been discussed.

**Keywords:** Central nervous system, multiple sclerosis, adipose-derived stem cell, cell transplantation

## Introduction

The term “demyelinating diseases” refers to a multiple group of nervous system diseases in which the myelin sheath of neuron is damaged which leads to reduction or loss of neural function [1]. Although the exact cause of these abnormal conditions is yet obscure, but some of them can be caused by genetics and environmental factors such as infectious agents, autoimmune reactions, inflammatory processes, hypoxic–ischaemic condition, focal compression and by unknown other factors.

Inflammatory demyelinating diseases include multiple sclerosis (MS) together with Devic’s disease (neuromyelitis optica) occur as a result of neurodegenerative processes in the central nervous system (CNS) [1]. Since Devic’s disease is probably a variant of MS. Thus, in the following we will focus on MS disease.

MS or the commonest of the demyelinating diseases, has been considered as the most important autoimmune demyelinating

disorder of the CNS which affects principally young adults and found in four clinical forms including: relapsing remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive relapsing MS (PRMS) [2] (Table 1).

MS can lead to neurological dysfunction as well as physical or cognitive disability including vision problems, numbness, fatigue, tremor, dizziness, vertigo, hearing loss, speech and swallowing problems, bowel and bladder dysfunction [3].

The principal pathological characteristics of MS are focal infiltration of auto reactive T cells and macrophages against myelin forming cells as well as components of myelin sheath, demyelination of axons, axonal loss, reduce myelin forming cells, vascular abnormalities, mitochondrial dysfunction, astrogliosis, and change in plasmalemma permeability and ion channels [4-6].

Howbeit the etiology of MS is yet unknown, but it appears to be linked to genetic predisposition including susceptible genes

**Table 1. The common subtype of multiple sclerosis and symptoms.**

Type of multiple sclerosis	MS course and symptoms
Relapsing remitting multiple sclerosis (RRMS)	RRMS is the most common subtype of multiple sclerosis which characterized by unpredictable acute attacks of immune cells on myelin and axons that followed by periods of remission. RRMS is accompanied with special symptoms including vision impairments, numbness, spasticity, fatigue, intestinal and urinary system problems
Primary progressive multiple sclerosis (PPMS)	PPMS largely affects the nerves of the spinal cord and is accompanied with special symptoms including stiff, weakness, and problems with balance
Secondary progressive multiple sclerosis (SPMS)	SPMS is considered as a second phase of the multiple sclerosis disease and is associated with increase in weakness, fatigue, stiff, Psychological impairment, mental disorders, intestinal and urinary system problems
Progressive relapsing multiple sclerosis (PRMS)	PRMS is the least common subtype of MS which is associated with double vision and eye pain, intestinal and urinary system dysfunction, dizziness, depression

in Human Leukocyte Antigen (HLA) region of Chromosome 6 such as HLA-DR2+ [7], HLA-DRB1 [8], DR15 [9], HLA-DQ6 [10], DQA 0102, combined with environmental influences such as exposure to viral and bacterial agents, vitamin D deficiency [11], smoking [12] and exposure to UV radiation.

Glucocorticoids and immunomodulating agents such as interferon beta and glatiramer acetate are conventional therapies for MS. These agents through special mechanisms such as prohibition of immune cell activation, anti-inflammatory cytokines secretion, decrease in matrix metalloproteinase activity, and increase the expression of Foxp3 in T regulatory cells [13] can partially alleviate the progression of this pathologic condition. Thus, more effective therapies using stem cells have been proposed by researchers. In this review, we summarized the comprehensive information about the cell based therapy for demyelinating disease. In addition we focused on beneficial effects of *in vivo* stem cells transplantation and discussed some of the characteristics and therapeutic effects of adipose-derived stem cells as an ideal cell source for cell based therapy in MS disease.

## Review

### Materials and methods

In this paper, the results of recent research in the field of cell-based therapies in treatment of demyelinating diseases were compared and among all stem cells sources, adipose tissue-derived stem cell (ADSCs) properties as one of the best source was discussed.

### Stem cells transplantation in demyelinating diseases

Stem cells are a population of undifferentiated biological cells that characterized by their self-renewal and ability to differentiate into other cell types. Mesenchymal stem cells (MSCs) which are a kind of non embryonic stem cells can be isolated from different tissues and widely used in the treatment of neurological disorders.

It has been shown that transplantation of human umbilical cord-derived MSCs (hUC-MSC) simultaneously with anti-inflammatory treatment in MS patients, leads to reduced expanded disability status scale scores, relapse occurrence and decreased in inflammatory cytokines production due to the significant increase in T helper (Th) 2 cells and decrease Th1 cells. Therefore, with regard to improvement overall symptoms, these cells may be a suitable cell source for treatment of MS [14].

In a recent study human embryonic and human bone-marrow-derived MSCs (hBM-MSCs and hES-MSCs) were transplanted into experimental autoimmune encephalitis (EAE) which is a mouse model of MS. The results of this study showed that hES-MSCs are a better cell source for MS treatment as compared with BM-MSCs due to high EAE disease-modifying effects and because of reduce clinical signs and neuronal demyelination [15]. Human wharton's jelly stem cell-derived oligodendrocyte progenitor cells, can also promote the regeneration of myelin sheaths in mice brain lesions and diminished the clinical signs of MS [16]. In addition, wharton's jelly-derived stromal cells (WJ-MSC) implantation into EAE model of MS, have neuroprotective effects which were parallel with a reduction in autoantigen-induced T cell proliferation that effectively modulated immune system responses. Thus, these effect suggesting that WJ-MSC may be a good cellular resource for cell transplantation to treat MS [17].

Available evidence indicates that pre-induced bone marrow MSC (with neurotrophin-3 and retinoic acid) transplantation combined with electro acupuncture treatment in demyelinated spinal cord (created by ethidium bromide) not only promoted MSC differentiation into oligodendrocyte-like cells, but also improved remyelination process which leads to sensorimotor functional recovery in the demyelinated spinal cord [18]. In addition, placental MSCs via reduced production of the anti-inflammatory proteins such as TNF- $\alpha$ - stimulated gene/protein 6 (TSG-6) in inflammatory regions, have therapeutic effects in mice with EAE [19]. Other studies have shown the therapeutic benefit of BM-MSCs [20,21], neural stem cell [22], oligoprogenitor (OP) like cells differentiated from spermatogonia [23], olfactory ensheathing cells [24] and embryonic stem cell-derived neural precursor cells [25] in animal models of demyelinating diseases.

In contrast with these studies, Nessler et al., showed that intravenously administration of human BM-MSCs has no effects on remyelination process and glial cell reactions in cuprizone model of MS because these cells were not able to cross the blood-brain barrier [26]. Thus, adipose-derived stem cell (ADSCs) as a suitable cell source has attracted attention

of many researchers due to the unique characteristics. In this review some of these characteristics have been discussed according to available information. In addition, the probable mechanisms responsible for the therapeutic effects of these cells on remyelination process also have been discussed.

Adipose tissue is an attractive source of a pluripotent progenitor cells which called adipose-derived stem cells (ADSCs). In the human body, there are different types of adipose tissue including white, brown, mammary, bone marrow and mechanical fat which are morphologically different and each type has distinct biological function. For example, the results of a previous study showed that the numbers and differentiation potential of ADSCs within white fat are higher than in brown fat [27]. Furthermore, Kalbermatten et al., in similar experiment reported that although ADSCs which isolated from both superficial and deep layer of human abdominal fat, express similar levels of the growth factors, but cell proliferation capacity of ADSCs that isolated from superficial layer is faster than those from other layers [28].

ADSCs are spindle-shaped cells with a fibroblast-like morphology which found in plentiful quantities (approximately 100,000 ADSCs per gram of fat tissue) [29] and can be isolated and cultured via a minimally invasive method according to our previous study [30] (Figure 1). These cells can be identified by the expression of MSCs markers including CD90, CD105, CD44 and pluripotent markers such as oct4 and nanog. In addition, these cells do not express hematopoietic or endothelial markers such as CD34, CD45, and CD14 [31-33]. ADSCs have

the ability to preserved their characteristics during repeated subculture and when cultured in the appropriate conditions are able to differentiated into other cells from different germ layers (Table 2) [31-36].

**Table 2. Adipose-derived stem cells differentiation into other cells by special inductive factors.**

Cell lineage	Inductive factors	References
Neurotrophic factor secreting cells	Basic fibroblast growth factor, Epidermal growth factor, Platelet-derived growth factor, L-glutamine, N2 supplement	[31,32]
Neuron cells	Basic fibroblast growth factor, Epidermal growth factor	[31,33]
Hepatocyte cells	Epidermal growth factor, Hepatocyte growth factor, Fibroblast growth factor	[34]
Chondrocyte cells	Transforming growth factor-β3, Linoleic acid, Insulin-transferrin-selenium, Ascorbate 2-phosphate	[35]
Schwann cells	Epidermal growth factor, Basic fibroblast growth factor, Platelet-derived growth factor, Forskolin	[31,36]

### How do ADSCs work?

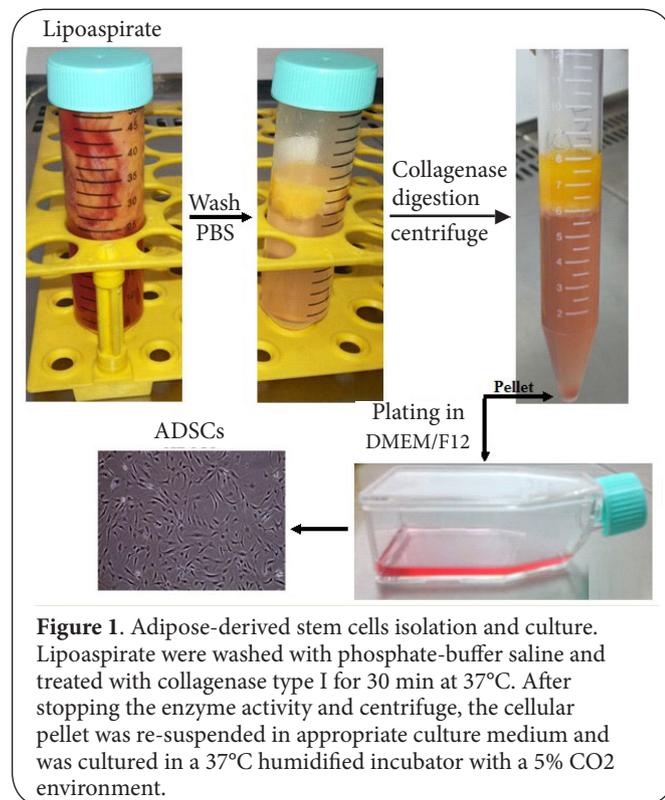
Recently, successful cell transplantation and important experimental results proposed considerable therapeutic potential of ADSCs for cellular replacement in MS. The results of our previous study suggested that human ADSCs may be an ideal cell source for regenerative cure because can ameliorate the neuropathological signs and improve motor function in lysophosphatidylcholine model of MS. Our finding further confirms that these cells may promote remyelination process by either differentiation into mature oligodendrocyte or indirectly by promoting the survival of endogenous precursor cells via production of neurotrophic factors [30].

In similar experiment Tomita et al., [37] also reported that ADSCs trans-differentiation into a Schwann cells phenotype cells (dASC) and transplantation in a rat model of chronic denervation, enhanced nerve regeneration and motor functional recovery through promote remyelination process.

Another study's results demonstrated that intravenous and intra-peritoneal ADSCs administration into EAE model of MS can greatly reduce attack immune cells into the CNS and ameliorate severity of clinical scores due to their immunomodulative and neuroprotective effects [38].

It has been reported that intravenous transplantation of ADSCs can play a significant role in tissue repair processes through migration to the lesion areas and suppression of inflammatory responses in chronic progressive and relapsing-remitting EAE models of MS [39].

In the other hand, Zhang et al., reported although infusion of wild type ADSCs (from EAE mice) has no therapeutic effects



on the disease progression, but these cells are able to improve the disease course of autoimmune mediated demyelination by the regulation of the inflammatory responses [40].

In accordance to all published data, ADSCs play a significant role in tissue repair processes by virtue of their ability to neuroprotective and immunomodulative effects as well as their ability to migrate into the lesion areas and differentiation to mature oligodendrocyte which promoted remyelination process. Hence, in the following, we will focus on the special properties of ADSCs which are involved in promoting nerve regeneration and remyelination process including migration and differentiation potential, paracrine-mediated neuroprotection, immunomodulatory and anti-inflammatory effects.

### **Mechanisms of potential utility of ADSCs**

Investigators have postulated that ADSCs migration and differentiation potential may be exclusive mechanisms which these cells used for repair and regenerate tissues.

Integrins or transmembrane receptors are one of the most important factors that are essential for cell migration. There are several subtypes of integrins which involved in a wide range of biological activities, such as immune patrolling and cell migration. Integrin  $\alpha 4\beta 1$  (or VLA-4) which expressed on leukocytes plasmalemma, by binding to its receptor on endothelium (VCAM-1), begins cell homing process. In addition, it has been demonstrated that this integrin also is expressed on ASCs, whereas not expressed in BM-MS [41-43]. Thus, for MSC-based therapy in MS disease, ADSCs are a better cell source because they are able to cross the blood-brain barrier (BBB) and exert their action including neuroregenerative, immunomodulatory and anti-inflammatory effects.

Since, the inflammation of the CNS due to focal immune

cells infiltration, is the primary cause of damage in MS patient, it is recommended that concomitant with ADSCs transplantation, anti-inflammatory drugs also used to reduced leukocytes homing.

Many of the identified growth factors such as neurotrophic, angiogenic and antiapoptotic factors can be secreted by ADSCs which play an important role in various cellular processes including cell proliferation, differentiation and maturation. Moreover, each of these growth factors exerts its biological activities through specific receptors [44-56] (Table 3).

As regards the short half-life of these growth factors as well as inability to cross the BBB when delivered peripherally, ADSCs transplantation instead of neurotrophic factors may be an ideal procedure for delivering these factors into demyelinating tissues.

These paracrine effects of ADSCs may be associated with modulation of immune responses via direct cell-to-cell interaction, increase the number of CD4+lymphocytes, reduce pro-inflammatory cytokine secretion and secrete prostaglandin E2, leukemia inhibitory factor and kynurenine [57,58].

Concurrent with the migration of stem cells to inflammation area, in addition to the release of growth factors and anti-inflammatory cytokines, these cells can also differentiate into oligodendrocyte cells. Moreover, ADSCs through paracrine effects are able to promote survival and proliferation of endogenous oligodendrocyte precursor cells which leading to further the process of remyelination. Another relevant finding of our previous study was that a high percentage of ADSCs which transplant in rat model of MS, expressed Olig2 and MBP that are special markers of oligodendrocyte [30]. Therefore, ADSCs may participate in remyelination process by differentiation into mature oligodendrocyte or by increasing

**Table 3. The different nerve growth factors which secreted by adipose-derived stem cells.**

Type of growth factors	Related receptor	Dependent function	References
Nerve growth factor (NGF)	TrkA, p75 NTR	This factor can promote the biosynthesis of myelin component sheaths in central and peripheral nerve system and affect on oligodendrocyte differentiation	[44,45]
Brain derived neurotrophic factor (BDNF)	TrkB, p75 NTR	This factor can prevent neuronal degeneration and improve neurological functional recovery after transplantation	[46-48]
Glial cell line-derived neurotrophic factor (GDNF)	GFR $\alpha$ 1, RET	This factor can prevent motor neuron degeneration and is a highly potent trophic factor for spinal motor neurons and central noradrenergic neurons	[49-51]
Vascular endothelial growth factor (VEGF)	VEGF receptor-2	This factors has angiogenesis activity	[52,53]
Basic fibroblast growth factor (bFGF)	FGFR1 to FGFR4	This factors has angiogenesis activity	
Hepatocyte growth factor (HGF)	C-Met receptor	This factors has angiogenesis activity	
Granulocyte macrophage-colony stimulating factor (GM-CSF)	GM-CSF-receptor	This factors has angiogenesis activity	
Transforming growth factor- $\beta$ (TGF- $\beta$ )	TGFB receptor1	This factor has anti-apoptosis activity	
Insulin-like growth factor-1 (IGF-1)	IGF1-R	This factor has anti-apoptosis and neuroprotection activity	[52-56]

the survival of endogenous precursor cells.

## Conclusion

ADSCs are an ideal cell source for stem cell based therapies in treatment of demyelinating disease such as MS. These cells may take part in promote remyelination by either differentiating into mature myelin forming cells or by secreting various nerve growth factors which can promoting neural cell survival and proliferation. A large number of studies with ADSCs transplantation have already performed and the results of these studies demonstrated that these cells are effective in demyelinating disease treatment. With respect to the differentiation potential of ADSCs and the ability of these cells in secretion of many nerve growth factors as well as the ability to pass the BBB, suggests that intravenous injection or direct transplantation of ADSCs is a supreme procedure to deliver cellular and nerve growth factors into injured tissue for MS treatment.

## List of abbreviations

ADSCs: Adipose-derived stem cells  
MS: Multiple sclerosis  
CNS: Central nervous system  
RRMS: Relapsing remitting MS  
PPMS: Primary progressive MS  
SPMS: Secondary progressive MS  
PRMS: Progressive relapsing MS  
HLA: Human Leukocyte Antigen  
MSCs: Mesenchymal stem cells  
hUC-MSC: Human umbilical cord-derived MSCs  
hES-MSCs: Human embryonic MSCs  
hBM-MSCs: Human bone-marrow-derived MSCs  
EAE: Experimental autoimmune encephalitis  
WJ-MSC: Wharton's jelly-derived stromal cells  
BBB: Blood-brain barrier

## Competing interests

The author declares that he has no competing interests.

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