



## Review Article

## Umbilical cord derived mesenchymal stem cell therapy for osteonecrosis of femoral head

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## ABSTRACT

Osteo Necrosis of the Femoral Head (ONFH) is a form of osteonecrosis that occurs owing to interruption of blood supply to the proximal femur followed by fragmentation, reossification, and remodelling of the femoral head. In United States, the incidence of avascular necrosis of the femoral head is projected to be around 30000, which contributes to 10% of the total hip replacement done every year. It was believed that necrosis of proximal femur occurs due to the inadequate supply of progenitor cells in the femoral head. So, treatment is aimed at introducing stem cells in necrosis area in order to avoid the risk of fracture and collapse to restore the structural design of femoral head. The objective of this review is to highlight the potential of mesenchymal stem cell (MSC) therapy along with core decompression for the management of ONFH with a special reference to umbilical cord-derived stem cells.

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## 1. Introduction

Osteo Necrosis of the Femoral Head (ONFH) is a form of osteonecrosis that occurs owing to interruption of blood supply to the proximal femur followed by fragmentation, reossification, and remodelling of the femoral head.<sup>1</sup> Head of the femur receives major its blood supply from the medial and lateral circumflex branches of the profunda femoris artery. Avascular necrosis of the femoral head, if not treated, will progress and lead to extensive worsening of the hip joint.<sup>2</sup> In United States, the incidence of avascular necrosis of the femoral head is projected to be around 30000, which contributes to 10% of the total hip replacement done every year. Prevalence is more common in men than women, with researches estimating it to be around 3 -5 to 1 percent.<sup>3</sup> Treatment of ONFH depends upon various factors like the age, occupation, stage of the avascular necrosis and the previous treatment. The most common cause for necrosis

of the femoral head includes fractures, dislocations, chronic steroid and alcohol use.

ONFH is a mixture of osteological and vascular disease of the hip joint.<sup>4</sup> Numerous researchers have suggested three important theories for ONFH namely a) thrombosis or embolism of functional capillaries which serve as the channel for stem cells, b) decline in the number of osteogenic cells, and mesenchymal stem cells in the infarcted region and c) apoptosis of osteogenic stem cells.<sup>5-7</sup> All these factors lead to insufficient bone repair and so the disease pathology progresses. Early stages of ONFH are managed by core decompression, bone grafting, and valgus osteotomy while in later stages, however, total hip arthroplasty (THA) is the treatment of choice. In younger people, though osteotomies are more likely to be the initial choice they are invariably followed by THA in the future. Improvement in pain and function have made this procedure treatment of choice. Core Decompression (CD) is used in the early pre-collapse stages of the disease to prevent the need for total hip arthroplasty (THA).<sup>8</sup>

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## 2. Regenerative therapy for ONFH

Regenerative medicine has grown enormously. Researchers have tried to use orthobiologic therapy for regeneration of femoral head necrosis. Autologous stem cells have given a promising result in controlling the progression of disease thereby preventing THA in younger people.<sup>9,10</sup> The idea of cell-based therapy deals with the usage of autologous or allogenic cells with a higher regenerative potential to heal the degenerative diseases of bone and joints. Studies have shown the excellent role of mesenchymal stem cell (MSC) from varied sources along with the core decompression technique in the management of ONFH.<sup>11–14</sup> Core decompression releases the intra-osseous pressure while MSCs regenerate the osteogenic cells and stimulate vasculogenesis thereby preserving the femoral head. The objective of this review is to highlight the capacity of umbilical cord-derived MSC therapy in conjunction with CD for the management of ONFH.

It was believed that necrosis of proximal femur occurs due to the inadequate supply of progenitor cells in the femoral head. So, treatment is aimed at introducing stem cells in necrosis area in order to avoid the risk of fracture and collapse to restore the structural design of femoral head. A study by Hernigou and Beaujean in 2002, first demonstrated a combined injection of mesenchymal stem cells in areas of necrosis along with core decompression. In his study which included 189 hips, only 65 proceeded to THA. In another study by Hernigou et al. which included 534 hips, 46% showed a reduction in the size of the lesion in MRI after stem cell transfer. These studies utilized bone marrow-derived stem cells. However, the concept of MSC therapy for ONFH was laid down by these pioneering studies. Zhao et al.<sup>15</sup> included 53 hips treated with MSC therapy and 75% showed a reduction in the size of the lesion in MRI, which proved the effectiveness of combining stem cells with other modalities of treatment.

## 3. Rationale behind cell therapy

Alcohol and steroid use are the most important causes of nontraumatic osteonecrosis. The pathogenesis behind this is the occlusion of small vessels by fat emboli impeding blood supply to the sinusoids, as a result of rise in intraosseous pressure due to fatty infiltration following steroid use.<sup>16</sup> Hernigou et al.<sup>17</sup> showed that a more favorable outcome could be obtained when patients receive a greater number of MSCs in the autologous bone marrow concentrate injection into the necrotic lesion. Few other studies also confirmed the same.<sup>9</sup> A retrospective study which presented the 10-year results of concentrated autologous bone marrow aspirate transplantation for osteonecrosis of the femoral head showed that MSC therapy can be employed as one of a joint-preserving treatment for ONFH.<sup>18</sup>

Mesenchymal Stem Cells from osteonecrosis patients revealed diminished survival, proliferation and differentiation, so measures have to be taken to enhance their efficiency.<sup>19</sup> One such measure is the influence of low oxygen on the differentiation of MSCs from osteonecrosis animals. Other steps include treatment with growth factors, hypoxic shock, and antiaging compounds.<sup>20</sup> Fan et al.<sup>21</sup> stated that MSCs from osteonecrosis rabbits revealed drastically diminished proliferation capacity, repressed expression of stemness genes, reduced osteoblasts formation, and increased adipocytes formation, implying an osteonecrosis-related impairment when compared with normal rabbit. Hypoxia through differential growth factor production, provides a favorable culture condition to promote proliferation as well as osteogenesis of MSCs.<sup>22</sup> Hence utilization of these MSC in the hypoxic niche would further enhance their regenerative and osteogenetic potential which favours the management of ONFH.

## 4. Sources of MSCs

Stem cells are the precursors of every organ and tissue in the body. The potentiality of the stem cells depends on their origin. Embryonic or pluripotent stem cells are present only at the earliest stages of development and adult or tissue-specific stem cells appear during fetal development and remain in our bodies throughout life. The most commonly used stem cell is Bone Marrow Stem Cells in ONFH, but adipose stem cells (ASCs) have the ability to promote angiogenesis. Jo WL et al.<sup>23</sup> showed that implanting both BMSC and ASC in the ONFH model of minipig considerably increases bone formation, in contrast to control group. Apart from these sources, allogeneic human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) and peripheral blood MSCs are also utilized in ONFH. Hence, selecting the ideal stem cell population and subpopulation reduce the risk of tumor formation and heterotopic ossification. According to Shimono et al.<sup>24</sup> mesenchymal stem cells with inhibited nuclear retinoic acid receptor- $\gamma$  did not undergo heterotopic ossification.

A three-year follow-up study by Chen et al.<sup>25</sup> used hUC-MSCs for the treatment of osteonecrosis of the femoral head. They assessed effective perfusion using the oxygen delivery index (ODI) and found that it increased after three days post-intervention. The necrotic volume of the femoral heads was significantly reduced as shown by MRI. hUC-MSCs differentiate into osteoblasts, thus preventing the spread of femoral head necrosis. Hence hUC-MSCs continue to hold a promise in being one of the productive sources of sub-population of MSCs utilized for cellular therapy for ONFH.

## 5. Patient Selection

The outcome of treatment not only depends on the mode of treatment but also upon the selection of patients. The Ficat and Arlet classified ONFH into IV stages based on the combination of plain radiographs, MRI, and clinical features.<sup>26</sup> Hauzeur et al.<sup>27</sup> study proved that the implantation of MSCs after core decompression did not stop the evolution of stage III ONFH. A randomized controlled trial by Sen et al.<sup>28</sup> showed that patients with adverse prognostic features at initial presentation like poor Harris Hip Score, X-ray changes, edema, and/or effusion on magnetic resonance imaging had significantly better clinical outcomes and hip survival. A preliminary study done by Houdek et al.<sup>29</sup> showed successful results when there is high nucleated cell count, and modified Kerboul grade was low. A preliminary study by Rastogi et al.<sup>30</sup> proved that autologous MSCs in avascular necrosis of the femoral head had a better outcome than bone marrow for the early stage of avascular necrosis of the femoral head. Hence earlier the patient is being treated with MSC therapy, the better the outcome achieved.

## 6. Safety Profile

There have been numerous studies explaining the benefits of stem cells in reducing the progression of avascular necrosis of the femoral head. But still, the safety of using these stem cells remains questionable. MSCs act by immunomodulatory and paracrine mechanisms. MSCs migrate to inflammatory sites and liberate bioactive molecules thereby controlling proinflammatory diseases.<sup>31</sup> A randomized controlled trial by Hare et al.<sup>32</sup> studied the effects of mesenchymal stem cells in patients with old myocardial infarction and found that adverse events were similar between both the case and control groups. A sub-study based on using cardiac magnetic resonance imaging added increased left ventricular ejection fraction in hMSC treated patients.

Lee et al.<sup>33</sup> studied the effects of mesenchymal stem cells in multiple system atrophy patients and concluded that MSCs delayed the progression of neurological deficits and had a better functional outcome than the control group. However, there are also studies stating that the immunosuppressive effect of MSCs was mediated by CD8+ regulatory cells and it favors tumor growth in allogeneic animals.<sup>34</sup>

A meta-analysis of RCTs and systematic overviews of similar meta-analysis concerning the efficiency and safety of stem cell therapy in osteonecrosis of the femoral head showed no significant differences in adverse events between the stem cell group and control group.<sup>14,35</sup>

## 7. Recent Advances

Exosomes are a group of vesicles derived from the multivesicular bodies. When they fuse with the plasma

membrane contents are released into the extracellular space. Recent research showed the effectiveness of exosomes on regenerative tissues.<sup>36</sup> Though mesenchymal stem cells have a diverse role in regeneration, to minimize the complications and to harness the paracrine effects of the stem cells and the progenitor cells, exosomes can be used as a cell-free treatment regime.

Exosomes obtained from stem cells mimic the phenotype of parent stem cells and so can be used in the treatment of various diseases. Stem cells like the hUC-MSCs are capable of secreting exosomes. Microvesicles released from stem cells exhibit a stem-cell-like phenotype to necrotic cells thereby activating self-regenerative programs.<sup>37</sup> Yu et al. showed that MSC-derived exosomes have a beneficial effect of preventing tumor growth and suppress angiogenesis by downregulating vascular endothelial growth factor (VEGF) mediated by the exosome-delivered miR-16 which would be of much use in the management of ONFH.<sup>38</sup>

## 8. Conclusion

MSC therapy for the management of osteonecrosis of the femoral head along with core decompression has given satisfactory response to be considered as the first-line management. hUC-MSCs remain a potential source of MSCs for the above treatment regimen. With the recent advances like exosomal therapy, the utility of MSC-derived exosomes of hUC-MSCs as a cell-free treatment option in the management of ONFH holds promise and needs further exploration in the future.

## 9. Conflict of Interest

The authors declare no potential conflict of interests.

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