Review Article

Bone Regeneration Therapy of Atraumatic Necrosis of Femoral Head

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Femoral head necrosis is a mobility disorder and till now no satisfactory solution has been reported. The principal contributing factor in the pathogenesis of the disease is insufficient blood supply to the femoral head resulting in necrosis of the femoral head. Various preventive measures required to treat femoral head necrosis include revascularization, adequate supply of osteogenic cells and establishing enough strength to avoid collapse. Among all, cell transplantation therapy is considered the most favourable treatment strategy for femoral head necrosis. However, the results merely depend on the etiology and the clinical stage of femoral head necrosis. Thus, it is better to make a treatment plan according to the epidemiology, disease status and stage. The main objective of this communication is to study the treatment of femoral head necrosis with cell replacement therapy and also its effects by focusing on the disease stages.

Key words: Femoral head necrosis, clinical stages, bone marrow transplant, cell-based therapy, radiographic evaluation, mesenchymal stem cells

Femoral head necrosis (FHN) is a mobility disorder, associated with hip joint[1,2]. According to an estimate, 70 % of the individuals diagnosed with FHN progress to develop the collapse of the femoral head. Thus, after 3 to 4 y of diagnosis, prosthetic joint replacement therapy is required for the stress-free movement[3,4]. FHN is not the disease of aging people, it is more prevalent in males aged between 30 to 40 y than females. It has also been documented fact that 75 % of cases of FHN are due to the involvement of bilateral joint[2]. Till now very little is known about the exact pathophysiology of the FHN. Although, a list of contributing factors such as sickle cell anaemia, use of steroids, femoral neck fractures are involved in the loss of osteogenic cells via obstructing blood supply especially in the greater trochanteric region[1,2]. Published opinions regarding this disease represent that there are 59 % of cases that proceed to symptomatic disease, which results in femoral head collapse[5]. The prognosis of the disease may vary differentially based on the causes and conditions of diseases. The risks of collapse in FHN increases due to many factors such as sickle cell anemia, which increase the risk of collapse up to 73 %. Similarly, the risk also increases due to an increase in alcohol consumption (47 %) and renal failure (46 %). Corticosteroid use also increases the risk of up to 26 % while atraumatic FHN is similar to the overall prevalence of bone collapse (38 %). HIV infected individuals have a lower risk of collapse due to FHN, about 15 %, and for lupus erythematosus patients the risk is relatively low at 7 % as compared to the overall occurrence of collapse due to FHN[5]. Thus, it is necessary to consider the disease-related etiological factors to make a treatment plan.

There are various methodologies adopted to treat FHN, which included surgical or non-surgical treatments. The disease progression with non-surgical treatment procedures has shown very limited success[2]. Therefore, the United States has decreased the use of early hip osteoarthritis surgery intended to preserve joint, which was considered as the most desirable treatment strategy in 25 % of FHN cases in 1992. Thus with time in 2008, only 12 % of cases underwent joint preserving procedures. However, at the same time total hip replacement increased from 1992 to 2008, an increase from 75 to 88 %[6].

Radiographic investigation for disease staging:

In order to classify FHN into different clinical stages, the Ficat and ARCO (Association Research Circulation

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Osseous) classification system was used, on the basis of radiographic evaluation of the femoral head. For that purpose, bone scintigraphy and magnetic resonance imaging (MRI), are used to understand the basic concept and compare the changes occur in each clinical stage of FHN[7-9]. These radiographic images are assessed from every aspect like anterior or posterior and then categorize into its specific stage. This information helps to comprehend the prognosis of FHN for the preparation of a basic treatment plan for the patients (Table 1)[10,11]. Thus FHN cases are categorized into 5 different stages. Stage 1 is considered as the earliest clinical stage in which the osteonecrotic lesions can be detected by bone scintigraphy and MRI. In this stage, osteonecrotic lesion show some marginal reaction on T1 weighed images and represents itself as a band of low signal intensity and on the other hand, T2 weighed images showed a band of high signal intensity.

Stage 2 occurs when clinical signs persist and radiograph shows definite areas of sclerosis with lucency on radiographs. In this stage, the necrotic portion is repaired by supplying adequate blood to the necrotic zone along with the deposition of dead cancellous bone towards the margin of the interface, which was generated by fibrous or laminar tissue during this process. In stage 3, the subchondral fracture seems in a different manner on the radiograph and looks like a crescent image. Thus stage 3 can be further subdivided into 3A and 3B in which if the collapse in the femoral head is <3 mm, it is 3A stage, while the 3B stage is when the collapse is ≥ 3 mm. Stage 4, the terminal stage causes narrow spacing in the osteoarthritic joints due to osteophyte formation. Thus Steinberg's classification clarified that after an advanced stage of stage 5 of osteoarthritis alteration in bones occurs at its maximum.

Specific Disease Investigation Committee (SDIC) explains FHN in terms of radiographic classification under the guidance of the Japanese Ministry of Health, Labour and Welfare that disease progresses represent the degree of weight put on the femoral head, adopted from a previous report (fig. 1). Radiographs are analyzed through three sites to find out the disease progression, these are anterior, plane and posterior. However, three different types of lesions are also explained to define the definite site of disease progression[9-11]. Type A lesion covers less surface almost one-third of the femoral head, on the other hand, type B lesion covers two-third of the weight-bearing surface. Similarly, type C occupies higher than two-third of the weight lifting area, which is further categorized into C1 and C2 lesions. C1 lesions do not spread anywhere while C2 lesions expand laterally to the border of the acetabulum. According to a published report, the risk of collapse for type A is 9 %, type B is 19 % and 59 % for type C.

Femoral head osteonecrosis treatment without using cells:

Several non-surgical treatment strategies are used to make a strain-free femoral head and limit disease advancement. These strategies include modification in activity, physical therapy and restriction of weight lifting[2]. When FHN gets initiated and reached at ARCO stage 1, the intramedullary pressure increases rapidly due to FHN thus the femoral head is drilled with core decompression method into a depth of 6 to 8 mm with the help of short trephine drill, which leads to decrease in intramedullary pressure of femoral head[7]. Core decompression treatment is a modern treatment strategy, which is much better than any conservative treatment. Core decompression treatment gave satisfactory results of 63.5 % at initial stages of FHN while conventional treatment methods gave only 22.7 % of results[11,12]. Still, the advantages associated with the core decompression method have been ignored[13,14]. However, the core decompression method only employed in initial stages and avoided in progressive stages of treatment. It was already documented that the

TABLE 1: ASSOCIATION RESEARCH CIRCULATION OSSEOUS (ARCO) AND STEINBERG STAGING OF BONE NECROSIS

Stages	Steinberg	ARCO
Stage I	Normal radiographs	Normal radiographs
Stage II	Sclerotic and cystic alterations	Sclerosis
Stage III	Subchondral collapse	Femoral head collapse, "crescent sign," no joint space narrowing, Collapse <3 mm (stage IIIA), Collapse >3 mm (stage IIIB)
Stage IV	Subchondral collapse, femoral head flattening, normal space between joints	Osteoarthritic deteriorative alterations
Stage V	Flattening and tightening of joint space, acetabular modifications	
Stage VI	Advanced degenerative alterations, Osteoarthritis	

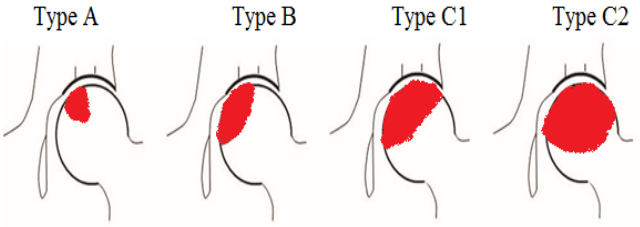

Fig. 1: Clinical staging of femoral head osteoarthritis
Radiography-based clinical staging of femoral head osteoarthritis, issued by the Japanese Ministry of Health, Labour and Welfare.

core decompression method gives different results at different clinical stages of FHN and could give adequate benefits. At Steinberg stage 3 of FHN, 29 % of patients recover with core decompression method, while at stage 3 and 4 of FHN 41 and 92 % of patients require arthroplasty, respectively[15]. When FHN progresses to an advanced stage, bone fragility becomes the most important criteria to be considered in spite of the intra-femoral pressure exerted on the femoral head.

In the advanced stage of FHN, chances of micro fractures of subchondral bone are increased, so it is mandatory to strengthen the initial bone health to avoid unfavourable circumstances[16].

Thus for this purpose vascularized bone grafts could play a vital role at advanced stages of FHN. When both arteries and veins are anastomosed during transplantation, approximately 90 % of the osteocytes survive and there is no osteoclastic resorption of the bone for incorporation. Vascularized bone grafts have been shown to be biomechanically superior. Thus, it is concluded that vascularized bone graft gives satisfactory results in an advanced stage of femoral head necrosis. In fact, use of vascular bone grafts in this advanced stage of FHN is a great difficulty. Another study stated the probable results of using vascularized bone grafts through a radiographic investigation. Thus, it is concluded that vascularized bone graft does not give satisfactory results in an advanced stage of femoral head necrosis[2,17-19].

Femoral head osteonecrosis treatment through bone-marrow transplantation:

The core decompression process is involved in decreasing intramedullary pressure along with an increase in the transport of living cells in a necrotic zone. Though FHN is not localized in a specific area, yet it disperses in the complete greater trochanteric area (GTA), which leads to a decrease in osteogenic cells throughout GTA[20,21]. Thus to increase the osteogenic cells in the trochanteric area, 2 other studies collaboratively described transplantation of concentrated bone marrow from the crest of the ilium using core decompression[22,23]. Thus, a study described that it is better to adopt concentrated bone marrow transplantation along with core decompression as compared to the decompression method alone especially in the initial stage of FHN as it can prolong the progress towards femoral head collapse. It was also reported that the collapse rate decrease with the use of bone marrow graft (10 %) while with the core decompression method alone the collapse rate was 63 %. After that, a series of studies were conducted, which focussed on the benefits of bone marrow grafting, which are discussed in fig. 2 and Table 2[23-28]. Thus the combinatory study of cell transplantation and core decompression gave acceptable results, which were further approved in clinical trials and were reported as a treatment strategy in of FHN in the initial stages, However, this combination was not approved to combat the collapse of the femoral head. A previous study thus linked different clinical stages of FHN with the effects of combined treatment and reported that 77, 74 and 0 % at stages 1, 2 and 3, respectively were prevented from collapse after combination therapy[22]. Thus, supplementary treatment is also applied to further increase the benefits associated with bone marrow grafts. Similarly, another study described the utilization of the technique of bone marrow graft along with platelet-rich plasma, which acts as an analgesic for 86 % of patients and prevents collapse in 79 % of patients. Afterward, another group of investigators used the technique of bone marrow transplantation with cancellous bone graft after core decompression method for both initial and advanced stage of FHN, which gave desirable clinical outcomes, according to which, the recovery rate was 80 % in stage 1 and 65.7 in stage 2, while in stage 3, the rate was 38.9 % and 33.3 % in stage 4. Thus the evidence obtained from this research study indicated that in the progressive stage of FHN, it is better to regain initial strength of the femoral head to avoid any fracture. Thus the initial strength can be achieved by bioactive scaffolding. In another study, FHN was treated at stages 1, 2 and 3A with concentrated bone marrow transplantation coupled with interconnected porous calcium hydroxyapatite. The results indicated that 56.7 % of cases did not advance towards collapse, while mild collapse was seen in 33.3 % of cases with <2 mm, however, 10 % of cases have collapse >2 mm. A previously reported study described treatment of patients in 2 treatment groups, one with porous hydroxyapatite in combination with bone marrow transplantation while in the other

treatment group hydroxyapatite was used alone at stage 2. The results indicated that 78.6 % of patients receiving combination treatment did not progress towards collapse as compared to 41.7 % of patients who were treated only with bone marrow graft. This study stated that histological study of the femoral head indicated that even after the clinical recovery of FHN, it still showed signs of osteomalacia and osteoporosis[29-35]. Thus this problem was described in a study that reported another technique of curettage of the necrotic zone despite the bone decompression method[36].

Femoral head osteonecrosis treatment through mesenchymal stromal cell transplantation:

When bone marrow graft and core decompression techniques failed to give desired results, but showed a lesser number of osteogenic cells in necrotic patients. According to reported study, individuals with a history of steroid or alcohol use or any organ transplant have lesser number of osteogenic cells present in bone marrow. Thus, to combat this situation MSCs were used[22].

MSCs are used to regrow musculoskeletal tissues. Morphologically MSCs are elongated-nucleated adherent cells, which are categorized into osteogenic cells, adipogenic cells and chondrogenic cells. These cells can proliferate which results in the production of a large number of cells. This proliferative property of cells can regenerate lost cells in the femoral region. MSCs also have the ability to distinguish the vascular and avascular endothelial cells. This ability to differentiate help MSCs to treat interrupted blood supply to the FHN zone. MSCs can be distinguished from other tissues and bone marrow. The ideal source for MSC differentiation and proliferation remains controversial. However, the strategy to draw bone marrow is relatively safe and effective[37-43].

Few studies reported the use of MSCs for treatment purposes in clinical trials and the results are shown in fig. 2 and Table 2. The comparison between transplanted cultured MSCs and bone marrow cells with core decompression in the initial stages of FHN have been documented. The findings showed that after 5 y only 4 % of FHN patients treated with MSCs advanced towards collapse while 23 % of patients treated with bone marrow transplant progressed towards collapse. A recent study also compared MSCs treatment with bone marrow transplant in both early and advanced stage of FHN, while another study did not find any variation in results regarding the collapse rate between both treatment groups in comparison to a reported study in which both treatment groups had 0 % collapse rate at initial stage 1, 18 % at stage 2 and at stage 3 the MSCs-treated group showed 20 % collapse rate in comparison to the bone marrow group with a collapse rate of 25 %. A different study also reported that MSCs with core decompression method is not adequate enough to

TABLE 2: USE OF CELLS WITH THE STAGE OF FEMORAL HEAD OSTEONECROSIS

Cell source	Surgical technique
Bone marrow cells	Core decompression
	Core decompression+bioderived material
	Core decompression+bioactive scaffold
	Curettage+bone graft
Mesenchymal stem cells (MSCs)	Core decompression
	Curettage+bone graft+bioactive scaffold

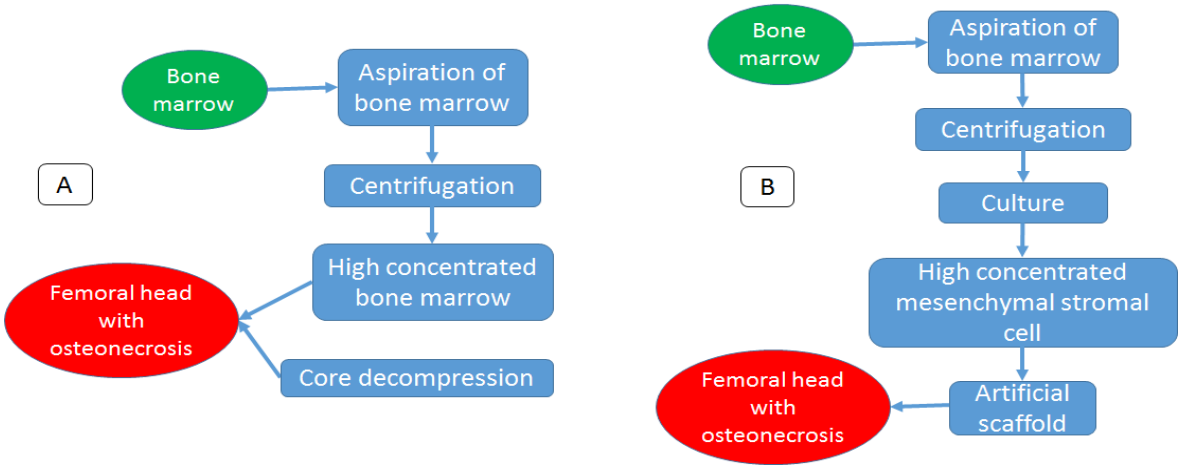

Fig. 2: Mechanism of cell-based treatment procedure in combination with bone marrow transplant
The mechanism of cell-based treatment procedure in combination with bone marrow transplant (A) The process of core decompression (B) Transplantation of mesenchymal stromal cells in combination with biomaterials after removal of necrotic bone.

prevent the collapse rate at an advanced stage of FHN. Similarly, two other groups adopted a different treatment plan for FHN patients and started to treat necrotic bone with the curette process along with packed beta-tricalcium phosphate in combination with mesenchymal stem cells and vascularized bone implant. It was documented that there was no collapse progression of hip shown at stage 3A in contrast to stage 3B, which showed a 50 % collapse progression. However, another study did not describe any advancement towards collapse at FHN stage III or IV[44-48].

Femoral head osteonecrosis treatment by using cells:

From the previous literature, it became evident the cells that can be distinguished from concentrated bone marrow cells (osteogenic) are beneficial for FHN treatment. Its preparation is easy and economical with low-risk, although, if the lesion is large and deep, a large number of cells are required. Condition and number of host tissue osteogenic cell is always a considerable factor for good results. Thus, the differentiation of MSCs into osteogenic cells and vascular endothelial cells assist in achieving benefits. MSCs use the cytokine and paracrine effect to produce a bulk of differentiated *in vitro* cell lineages. Though, the capability of differentiation of MSCs wholly depends on the age, medication and the health of the host[49-52]. Another treatment plan to treat FHN is the peripheral CD34-positive MSCs. These can be easily distinguished between vascular endothelial cells and osteogenic cells and can be prepared *in vitro* by induction of granulocyte colony-stimulating factors. In spite of various multiple sources of MSCs to treat osteonecrotic bone, bone remodelling being the subject of matter is the debatable topic. When talking about healthy tissue, there is always a balance between bone formation and resorption. While in a pathological condition of bone such as osteonecrosis, prolonged fracture repair, the balance between osteoclast and osteoblast is deregulated and reduced in number[35,53,54]. Thus, the necrotic bone should be removed to hasten recovery process. MSCs also have the ability to regulate osteoclastogenesis[55-57]. As a result, a healthy recovery of bone is achieved by the cytokine effect of MSCs.

Femoral head osteonecrosis treatment by using biomaterials:

The use of biomaterials has high clinical and social value to delay the total hip collapse. Presently biomaterials are upgraded to the extent that it can improve osteoinduction and osteoconduction in the femoral head[58,59]. In these biomaterials, porous tantalum rods gave outstanding results with improved osteoconductive property, its elasticity gives the consequences similar to human bone tissues[60]. Another study documented 50 cases of hips treated with tantalum rods and reported only 15.5 % of cases converted to total hip arthroplasty. Another study described the comparison of core decompression method vs. patients treated with tantalum rod implantation in its initial staged of FHN. After treatment, both groups showed improvements in the radiographic examination. Another group of the researcher used tantalum rods in an advanced stage of stage 2 and 3 of FHN, in combination with bone marrow and autologous bone grafts. After 5 y of treatment only 3 and 15 % of cases in stages II and III, respectively were further shifted to total hip replacement[61-63].

There are many other biodegradable materials used to treat FHN. These include nano-hydroxyapatite/ polyamide (n-HA/PA) 66 rods[61,64]. Another study described the treatment of 84 cases of FHN into 2 groups, one of which was treated with core decompression method along with incorporation of n-HA/PA 66 rods and the other one was treated with core decompression in combination with autologous cancellous bone graft. In the first group treated with n-HA/PA 66 rods, 21.1 % of patients progressed towards collapse as compared to bone grafting patients that showed 45.7 % of patients progressed towards femoral head collapse. Biomaterials have the elasticity of changing their morphology to fill cavities between bones, which are considered as one of the main advantages of biomaterials. There are a series of reports, which documented the use of various biomaterials in FHN patients. The researchers treated patients with porous hydroxyapatite rods; with composite filler, with porous beta-tricalcium phosphate granules along with cultured MSCs[31,32,47,48]. However, there are several benefits of using biomaterials in combination with the cell transplant method, still to observe the balance between degradation time and osteogenesis is an important consideration factor. Another influential factor is osteoclast, which influences the activity of biomaterials[65]. Biomaterials are responsible for the early resorption of bone as compared to bone formation, thus, as a result, it cannot prevent collapse. Consequently, the combinations with biomaterials should be analyzed closely.

Femoral head osteonecrosis treatment through growth factors:

FHN is a serious issue have been tried to resolve from ages with various treatment methods, incorporation of

growth factor is one of the popular treatment methods. These growth factors include platelet-derived growth factor, fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factors. The purpose of the usage of these growth factors is to improve revascularization and bone remodeling with FHN. Studies carried out on BMP-2 and BMP-6, it was stated that BMP-2 and BMP-6 if down-regulated in FHN patents can be used as a treatment purpose. The investigators treated patients with BMP-2 replacement along with allogenic fibula transplantation, concluded according to radiographic study that 17.6 % of FHN patients progressed to collapse at stages 2 and 3. The researchers treated FHN patients with two treatment groups, one of which is BMP-2 treatment along with artificial bone graft and the other one is the insertion of single artificial bone. The combinatory group of BMP-2 with artificial bone implants came up with a different percent of survival rate at different stages of FHN[66-69]. At ARCO 2b stage the survival rate was 100 %, at ARCO 2C stage the survival rate was 84.2 %, while at ARCO stage 3 the survival percentage was 30 %. While in comparison to the insertion of separate artificial bone the survival frequency for ARCO stages 2b, 2c, and 3 was 100, 76.5 and 37.5 %, respectively. Thus it was concluded that BMP-2 was much more beneficial. The researchers treated FHN patients with BMP-7 along with autologous, non-vascularized fibular grafts at Steinberg stage 2 and 3. After 4 y of treatment, it was found that a total of 29 % of patients advanced towards collapse. It was also concluded that this combination can also be used in short surgical procedures and rehabilitation period after surgery. Another study mentioned the treatment of patients in the initial stage of FHN and treated them with recombinant FGF-2 impregnated with gelatin hydrogel, thus after 1 y of treatment, 10 % of total hips advanced towards collapse. The researchers found a high level of interleukin-6 and tumor necrosis factor-α at an advanced stage of FHN. Thus it was found that cytokine activity accelerated when used in combination with growth factor, which can be further used in future studies[70-76].

CONCLUSION

FHN is a pathological process that progresses towards the collapse of the femoral head if untreated. In this review, various treatment strategies adopted by researchers were discussed to draw a conclusion. Thus conclusively delivery of osteogenic cells, revascularization and providing initial health to the femoral bone is included in the treatment plan to the challenges successfully. Thus new techniques should be developed into consideration with the pathology and clinical outcomes associated with these techniques.

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