

**Zhao D, Cui D, et al. Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. Bone. 2012;50(1):325-30.**

Design: randomized clinical trial

Purpose of study: to assess the effectiveness of bone marrow derived and cultured mesenchymal stem cells in the setting of core decompression for osteonecrosis of the femoral head

Population/sample size/setting:

- 100 patients (53 men, 47 women, mean age 33) treated for osteonecrosis of the femoral head at a university orthopedics department in China
- Eligibility criteria were age between 18 and 55 with osteonecrotic stages from IC to IIC according to the Association Research Circulation Osseous (ARCO) classification
  - o ARCO Stage 1 is MRI findings only; stage 2 is focal osteoporosis, cystic lesions, sclerosis; stage 3 is crescent sign (subchondral fracture); stage 4 is acetabular involvement
- Exclusion criteria were pregnancy, skeletal immaturity, previous infections, immunosuppressive drug therapy, a history of inflammatory arthritis, prior systemic corticosteroid treatment, and mental health problems

Interventions:

- All patients had core decompression (CD) with a trephine placed into the necrotic region of the femoral head, 2-3 mm away from the cartilage
  - o Both groups had similar rehabilitation programs postoperatively, with assisted weight bearing 3 weeks after the operation, graduating to full weight bearing 6 weeks after the operation
- Randomization was to CD alone (n=50 patients, 51 hips) or to CD plus bone marrow mesenchymal stem cells (BMMSC, n=50 patients, 53 hips)
  - o BMMSC were derived from taking 10 ml of subtrochanteric at the time that CD was done; this was cultured in vitro for two weeks and then injected, along with 2 ml of saline, into the osteonecrotic site through a previously prepared bone plug

Outcomes:

- Followup was done at 6, 12, 24, and 60 months after treatment,
- 7 patients were lost to followup in the CD group because of family relocation during the 5 years after surgery; followup was complete for the BMMSC group
  - o This left 44 hips in the CD group and 53 hips in the BMMSC group for analysis

- Primary outcome was radiographic progression of the osteonecrotic lesion at 60 months, done by radiologists who were unaware of group assignment
  - o Secondary measures were taken with the pain, function, activity, and motion subscores of the Harris Hip Score; other secondary measures were taken from the followup imaging by assessing the size of the osteonecrotic lesion
- 60 months after the index surgery, 10 of the 44 hips in the CD group had progressed to stage 3 or 4 on the ARCO scale; 5 of these hips underwent total hip replacement; the other 5 underwent vascularized bone grafting
- 60 months after the index surgery, only 2 of the 53 hips in the BMMSC group had progressed to stage 3, and both were treated with vascularized bone graft
- In addition to the lower rate of progression of the disease process, the BMMSC group had better Harris Hip scores and lower volumes of osteonecrotic tissue on MRI
- No surgical complications were seen in either group

Authors' conclusions:

- Compared with CD alone, BMMSC can significantly delay or avoid the progress of early-stage osteonecrosis of the hip
- A fairly small volume of subtrochanteric bone marrow may suffice for the source of the stem cells; previous studies have taken larger volumes from the iliac crest, but this may not be necessary

Comments:

- Randomization and blinding of principal outcomes are adequate and place the study at a low risk of bias for the main outcome
- Data for most of the secondary outcomes are reported using graphs and p values rather than numerically in tabular form, making it difficult to quantify them, but the main effect of the number of hips which progress to advanced disease is reported numerically and is a large effect
- There is one unclear issue in the exclusion/inclusion criteria; corticosteroid treatment was listed among the risk factors that would qualify a patient for inclusion, but the exclusion criteria included systemic corticosteroid treatment; in any event, there were a significant number of steroid treated patients in each group
- The details of the in vitro marrow cultivation may be too scant to make them reproducible, but these details may not be essential for the essentials of the study to be reproduced
- Table 1 has a clear error: for the proportion of patients at stage IIA, the p value is 1.165; p values can never exceed 1, which is the appropriate p value for that item
- Trials of this intervention are registered at [clinicaltrials.gov](http://clinicaltrials.gov), but none are being done in the United States; most are being done in Europe, with some in East Asia and one in Iran; the reasons for this are not clear

Assessment: adequate for some evidence that in the setting of core decompression, the use of bone marrow derived mesenchymal stem cells, taken from subtrochanteric marrow, cultured in vitro for two weeks, and implanted back into the necrotic lesion, greatly reduces the rate of progression of the disease process over the following five years, and similarly reduces the need for total hip replacement