Hip osteonecrosis: stem cells for life or behead and arthroplasty?

Philippe Hernigou¹ · Gildasio Daltro² · Jacques Hernigou³

Received: 3 June 2018 / Accepted: 4 June 2018 / Published online: 8 June 2018
© SICOT aisbl 2018, corrected publication June/2018

Philippe Hernigou

Gildasio Daltro

Jacques Hernigou

Approximately 5000 new patients with hip osteonecrosis are diagnosed each year in the France and 10,000 to 20,000 new patients in the USA. Almost two thirds of patients with hip osteonecrosis are between 30 to 60 years of age; as consequence, there are around 500,000 people in Europe and 500,000 others in the USA living with the disease or its consequence (hip arthroplasty). Considering its frequency in East Asian countries (China, Japan, Korea) where osteonecrosis is the most or second most common cause of total hip arthroplasty (THA), and considering the fact that the first genetic disease (sickle cell disease) in the world is a frequent cause of hip osteonecrosis in Africa, in India, and in Brazil, probably, the disease affects at least five million people across the globe. With this issue, we present papers from most of the geographic parts of the world.

The original version of this article was revised: There is an error in the original publication for the photos of the Guest Editors were not included.

✉ Philippe Hernigou
philippe.hernigou@wanadoo.fr

¹ Hôpital Henri Mondor, 94010 Créteil, France

² Federal University of Bahia, Salvador, Brazil

³ Epicura Hospital, Baudour and Hornu Belgium, Baudour, Belgium

Generalities on osteonecrosis

Risk factors include habitus as alcohol abuse, smoking, but also medications as steroid use. Corticosteroid treatment [1] remains one of the most frequent causes of osteonecrosis in the world as explained in some papers of this issue. Other potential etiologies for osteonecrosis concern diseases including sickle cell anemia [2], systemic lupus erythematosus, coagulopathy, human immunodeficiency virus (HIV) infection, hyperlipidemia, fat embolus syndrome, chemotherapy and/or radiation, organ transplantation, Gaucher disease, gout, and metabolic bone disease. The real pathogenesis of osteonecrosis (ON) still is unknown and many hypotheses are on research. Among many hypotheses regarding pathogenesis [3–8], new options factors as genetic and molecular factors are evaluated. The femoral head is the most frequent site of osteonecrosis; however, other locations as shoulder [9], knee [10], and talus are not uncommon. There are several animal models [11] for osteonecrosis as for bone defects that can mimic the human form of osteonecrosis. As regards to collapse, bipedal animal models seem more promising than quadrupedal animal models, but quadrupeds can also show marrow and bone cell death and can be used to study the repairs of bone defects [12, 13]. Medical treatment is rarely successful, but some success has been reported [14]. Early diagnosis and early-stage

osteonecrosis treatment are necessary. A timely overview of the problem, by clearly outlining current knowledge on classification is presented by Steinberg et al. [15] and evidence gaps in hip osteonecrosis treatment is described by Larson et al. [16].

Risk of collapse and quality of life

Hip osteonecrosis is associated with high hospitalization rates in surgery (around 90% of affected hips) due to a frequent natural evolution to collapse and subsequent hip arthroplasty. Hence, preventing the progression toward collapse is perhaps one of the most important challenges in hip surgery. Occurrence of collapse remains difficult to predict. Radiologic [17–20] and biologic [21] markers, site of necrosis, volume of osteonecrosis, and etiology of osteonecrosis are discussed in this issue.

Bilateral hip osteonecrosis is a condition that affects the quality of life [22, 23] in patients with osteonecrosis of the femoral head. Males are affected up to three times more than females. This disease is bilateral in 70% of patients who are around 40 years old, i.e., at the maximum of their productive years. Surgery performed on each side may have a deleterious effect on their workforce and subsequently on the economics. This explains that despite favourable results have been reported, osteotomies and vascularized grafts [24] are used less frequently in Western countries.

Core decompression and mechanical adjuvant to prevent collapse

Core decompression is the older conservative treatment; however, although core decompression is commonly performed in Western countries, it is seldom performed in Japan and Korea as surgeons are uncertain about the benefits [25]. It is true that the results of core decompression alone are confusing: considering that small lesions do not progress or progress slowly without any intervention and the fact that core decompression shows better outcomes in hips with small early lesions, core decompression alone might be considered sometimes as a treatment that is not so efficient; however, it provides symptomatic relief, and it appears to prevent collapse in early stages. Some authors have associated core decompression to bone substitute or tantalum implants [26–29].

Total hip arthroplasty and osteonecrosis

Once collapse has occurred, total hip arthroplasty remains the main treatment. The long-term outcome of implants in these patients is the major concern. Patients with arthroplasty related to osteonecrosis have the reputation to have inferior outcomes compared to those with primary osteoarthritis. These

unsatisfactory outcomes can be attributed to the usual patient's young age, but also the associated diseases that are the cause of osteonecrosis as corticosteroids and sickle cell disease. Interestingly, recent reports [30, 31] seem to demonstrate that the risk of revision of arthroplasty in osteonecrosis is not as high as suspected at least during the first 10 years of follow-up. Furthermore, lower rates of revision are noted with systemic lupus erythematosus [32] where a lower level of activity of the patient is probably observed. Most of hip arthroplasties when performed in young people will need revisions and these revisions are associated with bone loss and osteopenia; the quality and quantity of bone stock is a problem in these patients with higher risk of periprosthetic fractures in the long term with associated osteolysis when PE is used as bearing surface. Ceramic-on-ceramic [33] appears to prevent this problem. Other new technologies as short stems [34, 35] also are now in evaluation in the indication of osteonecrosis to preserve bone stock. Another aspect to consider is that patients may have had some operations before the THA or may have wait a long time before arthroplasty which may in some circumstances worsen the functional result [36].

Cell therapy and osteonecrosis

Almost three decades ago [37], it was postulated that bone marrow stem cells (BMSC) could be used to repair the osteonecrosis by “virtue” of their unique ability to boost angiogenesis and tissue repair. The pioneering report by Hernigou was the first study suggesting that injection of BMSC in the femoral head was a safe approach able to improve early stages of hip osteonecrosis. Since then, pre-clinical studies and human studies employing unselected BM-derived cells, circulating angiogenic cells, and mesenchymal stem cells have shown that injection of those cells to the femoral head was able to ameliorate hip performance. Andriolo et al. [38] confirm with a systematic review and meta-analysis that regenerative therapies increase survivorship of avascular necrosis of the femoral head, which is confirmed by Hernigou et al. [39] who report a prospective, randomized trial investigating long-term effects of bone marrow cell therapy in patients with bilateral osteonecrosis.

However, after almost 20 years of intensive clinical research in this field, we are still far from having drawn all the conclusions on the indications of cell therapy-based approaches in regenerating hip osteonecrosis. The authors [37, 40–44] of this issue critically address specific problems—namely cell quality and competence, and microenvironmental changes occurring at the bone osteonecrosis level. BMSC—which are supposed to be “functionally competent”—are often being collected from the BM of patients with bone disease and concomitant risk factors for bone marrow disease (corticosteroids, alcohol abuse...). In other words, we are reinfusing in most cases dysfunctional BMSC in our patients. On the other side, the recipient organ is

a “diseased” bone where several alterations have already occurred (i.e., altered immune response, inflammation, oxidative stress), thus reducing our chances of cell engraftment or angiogenic response (for those cells which mostly act via a paracrine manner). Indeed, we can suspect that only a very small proportion of the administered cells are engrafted by the osteonecrotic bone due to insufficient perfusion, microvascular dysfunction, and recipient’s immune system as in Lupus erythematosus, or abnormal biodistribution. The main questions concerning cell competence are (1) what really makes sometimes bone marrow mesenchymal stem cells (BMMSC) unable to exert their regenerative properties when reinjected in humans with as consequence failures particularly in late stages of osteonecrosis? (2) How can we achieve a permanent correction of maladaptive processes occurred in those cells? Recent work has suggested that BMMSC from some patients may carry significant epigenomic alterations which may substantially alter gene expression trajectories and cell functionality over the life time, regardless of the genetic background. Macro- (lifestyle, pollution, smoking) and microenvironmental stimuli (in situ changes of bone physiology) can explain probably some alterations in the repair. Cell therapy in osteonecrosis has attracted both scientific and public interests as an innovation that could alter the natural history of progression to collapse and to arthroplasty. Therefore, the clinical applications of cell-based therapies in patients with osteonecrosis will continue to be a challenge for patient selection, cell administration, and study design. The cost-effectiveness and the socioeconomic impacts of bone cell therapy in osteonecrosis will also need evaluation, but this will take time (several decades) since this should be compared to the long-term results or arthroplasties with their risk of revision and re-revisions in young patients as explained by the paper of Hernigou et al. [39]. In vitro expanded stem cells could be a solution to increase the number of cells as explained in another paper. But, will healthcare systems be able to afford costs related to procedure standardization, equipped labs for cell isolation and reprogramming, and availability of sophisticated delivery tools?

We conclude by thanking all the authors for taking time to contribute to this special issue on bone osteonecrosis. We apologize for those who submitted papers that were accepted but could not be included in this special issue; their articles will arrive quickly in the following issues of the Journal. We were very honored and privileged to take part in the organization of this special issue. We would like to express our sincere appreciation to Marius Scarlat, Editor in Chief of International Orthopaedics, and his editorial staff for their support for this special issue.

References

1. Zhao D (2018) Early diagnosis and treatment of steroid-induced osteonecrosis of the femoral head. INOR-D-18-00966
2. Daltro G, Franco BA, Faleiro TB, Rosário DAV, Daltro PB, Fortuna V Osteonecrosis in sickle cell disease patients from Bahia, Brazil: a cross-sectional study. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3905-z>
3. Luo P, Gao F, Han J, Sun W, Li Z (2018) The role of autophagy in steroid necrosis of the femoral head: a comprehensive research review. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3994-8>
4. Kao GS, Tu YK, Sung PH, Wang FS, Lu YD, Wu CT, Lin RLC, Yip HK, Lee MS (2018) MicroRNA-mediated interacting circuits predict hypoxia and inhibited osteogenesis of stem cells, and dysregulated angiogenesis are involved in osteonecrosis of the femoral head. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3895-x>
5. Peng Y, Liu Y, Huang D, Huang W, Shao Z (2018) Association of TNF- α -308(G/A) and -238(G/A) polymorphisms with non-traumatic osteonecrosis of the femoral head risks: a meta-analysis. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3859-1>
6. Nakahara E, Zhu W, Pezzotti G, Hamada H, Takao M, Sakai T, Sugano N (2018) Raman spectroscopy reveals differences in molecular structure between human femoral heads affected by steroid-associated and alcohol-associated osteonecrosis. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3898-7>
7. Nakahara E, Zhu W, Pezzotti G, Hamada H, Takao M, Sakai T, Sugano N (2018) Correction to: Raman spectroscopy reveals differences in molecular structure between human femoral heads affected by steroid-associated and alcohol-associated osteonecrosis. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3948-1>
8. Tian L, Baek SH, Jang J, Kim SY (2018) Imbalanced bone turnover markers and low bone mineral density in patients with osteonecrosis of the femoral head. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3902-2>
9. Colegate-Stone TJ, Aggarwal S, Karuppaiah K, Tavakkolizadeh A, Sinha J, Reichert IL (2018) The staged management of glenohumeral joint osteonecrosis in patients with haematological-induced disease-a cohort review. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3957-0>
10. Bhatnagar N, Sharma S, Gautam VK, Kumar A, Tiwari A (2018) Characteristics, management, and outcomes of spontaneous osteonecrosis of the knee in Indian population. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3878-y>
11. Xu J, Gong H, Lu S, Deasey MJ, Cui Q (2018) Animal models of steroid-induced osteonecrosis of the femoral head—a comprehensive research review up to 2018. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3956-1>
12. Wang Q, Zhang H, Gan H, Wang H, Li Q, Wang Z (2018) Application of combined porous tantalum scaffolds loaded with bone morphogenetic protein 7 to repair of osteochondral defect in rabbits. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3800-7>
13. Hernigou J et al (2018) Effects of press-fit biphasic (collagen and HA/ β TCP) scaffold with cell-based therapy on cartilage and subchondral bone repair knee defect in rabbits Jacques INOR-S-18-00984
14. Wang W, Zhang N, Guo W, Gao F (2018) Combined pharmacotherapy for osteonecrosis of the femoral head after severe acute respiratory syndrome and interstitial pneumonia: two and a half to fourteen year follow-up. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3907-x>
15. Steinberg ME, Oh SC, Khoury V, Udupa JK, Steinberg DR (2018) Lesion size measurement in femoral head necrosis. *Int Orthop* (Apr 25). <https://doi.org/10.1007/s00264-018-3912-0>
16. Larson E, Jones LC, Goodman SB, Koo KH, Cui Q (2018) Early-stage osteonecrosis of the femoral head: where are we and where are we going in year 2018? *Int Orthop*. <https://doi.org/10.1007/s00264-018-3917-8>
17. Gao F, Han J, He Z, Li Z (2018) Radiological analysis of cystic lesion in osteonecrosis of the femoral head. *Int Orthop* (Apr 27). <https://doi.org/10.1007/s00264-018-3958-z>

18. Hamada H, Takao M, Sakai T, Sugano N (2018) Subchondral fracture begins from the bone resorption area in osteonecrosis of the femoral head: a micro-computerised tomography study. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3879-x>
19. Wu W, He W, Wei QS, Chen ZQ, Gao DW, Chen P, Zhang QW, Fang B, Chen LL, Li BL (2018) Prognostic analysis of different morphology of the necrotic-viable interface in osteonecrosis of the femoral head. *Int Orthop* 42(1):133–139. <https://doi.org/10.1007/s00264-017-3679-8>
20. Kubo Y, Motomura G, Ikemura S, Sonoda K, Hatanaka H, Utsunomiya T, Baba S, Nakashima Y (2018) The effect of the anterior boundary of necrotic lesion on the occurrence of collapse in osteonecrosis of the femoral head. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3836-8>
21. Chen XJ, Yang F, Chen ZQ, He MC, Hong GJ, Huang JY, Zhou YC, Qin YX, Wei QS, He W (2018) Association of reduced sclerostin expression with collapse process in patients with osteonecrosis of the femoral head. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3979-7>
22. Uesugi Y, Sakai T, Seki T, Hayashi S, Nakamura J, Inaba Y, Takahashi D, Sasaki K, Motomura G, Mashima N, Kabata T, Sudo A, Jinno T, Ando W, Nagoya S, Yamamoto K, Nakasone S, Ito H, Yamamoto T, Sugano N (2018) Quality of life of patients with osteonecrosis of the femoral head: a multicentre study. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3897-8>
23. Osawa Y, Seki T, Takegami Y, Kasai T, Higuchi Y, Ishiguro N (2018) Do femoral head collapse and the contralateral condition affect patient-reported quality of life and referral pain in patients with osteonecrosis of the femoral head? *Int Orthop*. <https://doi.org/10.1007/s00264-018-3867-1>
24. Cho KJ, Park KS, Yoon TR (2018) Muscle pedicle bone grafting using the anterior one-third of the gluteus medius attached to the greater trochanter for treatment of Association Research Circulation Osseous stage II osteonecrosis of the femoral head. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3839-5>
25. Yoon BH, Lee YK, Kim KC, Ha YC, Koo KH (2018) No differences in the efficacy among various core decompression modalities and non-operative treatment: a network meta-analysis. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3977-9>
26. Sionek A, Czwojdzinski A, Kowalczewski J, Okoń T, Marczak D, Sibiński M, Złotorowicz M, Czubak J (2018) Hip osteonecroses treated with calcium sulfate-calcium phosphate bone graft substitute have different results according to the cause of osteonecrosis: alcohol abuse or corticosteroid-induced. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3892-0>
27. Hu R, Lei P, Li B, Liu H, Yang X, Wen T, Hu Y, Tian X (2018) Real-time computerised tomography assisted porous tantalum implant in ARCO stage I-II non-traumatic osteonecrosis of the femoral head: minimum five-year follow up. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3899-6>
28. Lu Y, Lu X, Li M, Chen X, Liu Y, Feng X, Yu J, Zhang C, Niu D, Wang S, Wang Z, Lu J (2018) Minimally invasive treatment for osteonecrosis of the femoral head with angioconductive bioceramic rod. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3919-6>
29. Aurégan JC, Villain B, Bégué T (2018) What is the rate of patients undergoing a total hip arthroplasty after core decompression and insertion of a tantalum rod in osteonecrosis of the femoral head: a systematic review. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3961-4>
30. Osawa Y, Seki T, Takegami Y, Kusano T, Makida K, Ishiguro N (2018) Cementless total hip arthroplasty for osteonecrosis and osteoarthritis produce similar results at ten years follow-up when matched for age and gender. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3987-7>
31. Kobayashi S, Kubo T, Iwamoto Y, Fukushima W, Sugano N (2018) Nationwide multicenter follow-up cohort study of hip arthroplasties performed for osteonecrosis of the femoral head. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3980-1>
32. Chen DQ, Cancienne JM, Werner BC, Cui Q (2018) Is osteonecrosis due to systemic lupus erythematosus associated with increased risk of complications following total hip arthroplasty? *Int Orthop*. <https://doi.org/10.1007/s00264-018-3871-5>
33. Hernigou P, Auregan JC, Bastard C, Housset V, Flouzat-Lachaniette CH, Dubory A (2018) Higher prevalence of periprosthetic fractures with ceramic on polyethylene hip bearing compared with ceramic on ceramic on the contralateral side: a forty year experience with hip osteonecrosis. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3863-5>
34. Mersch D, Häne R, Tohidnezhad M, Pufe T, Drescher W (2018) Bone-preserving total hip arthroplasty in avascular necrosis of the hip—a matched-pairs analysis. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3896-9>
35. Miladi M, Villain B, Mebtouche N, Bégué T, Aurégan JC (2018) Interest of short implants in hip arthroplasty for osteonecrosis of the femoral head: comparative study “uncemented short” vs “cemented conventional” femoral stems. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3981-0>
36. Jo WL, Lee YK, Ha YC, Kim TY, Koo KH (2018) Delay of total hip arthroplasty to advanced stage worsens post-operative hip motion in patients with femoral head osteonecrosis. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3952-5>
37. Hernigou P, Guerin G, Homma Y, Dubory A, Chevallier N, Rouard H, Flouzat Lachaniette CH (2018) History of concentrated or expanded mesenchymal stem cells for hip osteonecrosis: is there a target number for osteonecrosis repair? *Int Orthop*. <https://doi.org/10.1007/s00264-018-4000-1>
38. Andriolo L, Merli G, Tobar C, Altamura SA, Kon E, Filardo G (2018) Regenerative therapies increase survivorship of avascular necrosis of the femoral head: a systematic review and meta-analysis. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3787-0>
39. Hernigou P, Dubory A, Homma Y, Guissou I, Flouzat Lachaniette CH, Chevallier N, Rouard H (2018) Cell therapy versus simultaneous contralateral decompression in symptomatic corticosteroid osteonecrosis: a thirty year follow-up prospective randomized study of one hundred and twenty five adult patients. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3941-8>
40. Goodman SB (2018) The biological basis for concentrated iliac crest aspirate to enhance core decompression in the treatment of osteonecrosis. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3830-1>
41. Liu L, Gao F, Sun W, Wang Y, Zhang Q, Wang B, Cheng L, Li ZR (2018) Investigating clinical failure of core decompression with autologous bone marrow mononuclear cells grafting for the treatment of non-traumatic osteonecrosis of the femoral head. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3918-7>
42. Tomaru Y, Yoshioka T, Sugaya H, Shimizu Y, Aoto K, Wada H, Akaogi H, Yamazaki M, Mishima H (2018) Mid-term results of concentrated autologous bone marrow aspirate transplantation for corticosteroid-associated osteonecrosis of the femoral head in systemic lupus erythematosus. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3959-y>
43. Hauzeur JP, De Maertelaer V, Baudoux E, Malaise M, Beguin Y, Gangji V (2017, 2017) Inefficacy of autologous bone marrow concentrate in stage three osteonecrosis: a randomized controlled double-blind trial. *Int Orthop*. <https://doi.org/10.1007/s00264-017-3650-8>
44. Hernigou P, Thiebaut B, Housset V, Bastard C, Homma Y, Chaib Y, Flouzat Lachaniette CH (2018) Stem cell therapy in bilateral osteonecrosis: computer-assisted surgery versus conventional fluoroscopic technique on the contralateral side. *Int Orthop*. <https://doi.org/10.1007/s00264-018-3953-4>