Clin Orthop Relat Res (2017) 475:2241–2244 / DOI 10.1007/s11999-017-5425-3

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

Published online: 22 June 2017

CORR Insights

CORR Insights®: Free Vascularized Fibular Grafting Improves Vascularity Compared With Core Decompression in Femoral Head Osteonecrosis: A Randomized Clinical Trial

Anton Plakseychuk MD, PhD

Where Are We Now?

For many years, core decompression was generally considered a mainstay of treatment for avascular necrosis (AVN) of the femoral head [4, 5]. But more than 20 years ago, multiple studies [7, 17] demonstrated that this procedure has a limited success rate and is probably best used in patients with small, early AVN lesions. At the same time, free vascularized fibula graft, a complex and labor intensive procedure that requires microsurgical anastamosis of the vessels [18, 19], saw wider use. Because of the complexity of free vascularized fibula graft surgery, and in order to perform it efficiently, the procedure is often done using two teams of surgeons working simultaneously, an impractical proposition for community hospitals. For that reason, most of them continue to perform core decompression today [14, 16].

Although free vascularized fibula grafting is considered superior to simple core decompression [6, 13], the risk of failure still correlates directly to the size and location of the lesion [3]. Currently, an AVN lesion about 50% of the femoral head, located close to the articular surface in superior aspect of the head, cannot be successfully treated by any existing femoral head preservation technique. Although vascularized fibula grafting may delay the progression of AVN by providing structural support to—and revascularization of—the femoral head, it has been my observation that in time, even a successful procedure eventually is followed by deterioration of the cartilage immediately over the lesion. This may be a function of the original insult and the subsequent lack of normal diffusion.

It has been my experience that free vascularized fibula grafting increases vascularity of the femoral head—but by how much remains difficult to measure. The current study by Cao and colleagues addresses some of these

This CORR Insights® *is a commentary on the article* "Free Vascularized Fibular Grafting Improves Vascularity Compared With Core Decompression in Femoral Head Osteonecrosis: A Randomized Clinical Trial" *by Cao and colleagues available at:* DOI: 10.1007/s11999-017-5374-x.

The author certifies that neither he, nor any members of his immediate family, have any commercial associations (such as consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research*® editors and board members are on file with the publication and can be viewed on request.

The opinions expressed are those of the writers, and do not reflect the opinion or policy of *CORR*® or The Association of Bone and Joint Surgeons®.

This *CORR* Insights® comment refers to the article available at DOI: 10.1007/s11999-017-5374-x.

A. Plakseychuk MD, PhD (✉)
Bone and Joint Center, Magee Women's Hospital of University of Pittsburgh Medical Center, 300 Halket Street, S 1600, Pittsburgh, PA 15213, USA
e-mail: antonp@pitt.edu

CORR Insights

issues in a prospective, randomized trial that compares core decompression and free vascularized fibula graft in terms of improved vascularity of the femoral head, progression of disease, and hip scores.

Where Do We Need to Go?

Recently, surgeons have considered combining core decompression with cultured or concentrated bone mesenchymal stem cells [15, 22]—peripheral blood stem cells mobilized by granulocyte-colony stimulating factor [11] or bone morphogenetic proteins [8, 9]—to enhance bone repair in AVN. But the clinical success in those studies was inconsistent (from 47% to 83%) [1]. Still, the use of autologous cell therapy in combination with core decompression appears to be superior to core decompression treatment alone [12]. Further blinded, randomized, controlled trials are needed to clarify these results.

Surgical intervention alone would not cure AVN. Femoral head ischemia results in the collapse of articular cartilage into the necrotic area, due to an imbalanced osteoclast-mediated bone-remodeling process. Osteoclast activity is regulated by osteoprotegerin, the receptor activator of NF-kB Ligand (RANKL), and the NK-kb (RANK) system. Tissue samples in patients with AVN demonstrated upregulation of RANKL, RANK mRNA, and down-regulation of OPG mRNA [21]. Understanding the clinical utility of serum OPG and RANKL levels as markers of the AVN activity requires further investigation.

Although we know the multiple etiological factors associated with AVN (long-term hormone therapy, trauma, and alcoholism, among others), we still do not understand why only certain patients with those factors actually develop AVN. In recent years, it was proved that the genetic polymorphisms of plasminogen activator inhibitor-l (PAI-1) gene [10], apolipoprotein A1 (apoA 1) gene [20], and apoA5 gene [2] were associated with AVN of the femoral head. The PAI-1 gene, which regulates the fibrinolysis system, is composed of 379 amino acids and locates in human chromosome 7q21.3-q22. The primary function is to reduce the fibrin degradation of protein aggregation and maintain the normal dynamic balance of coagulation and fibrinolysis system in the natural blood circulation. Does hypercoagulation lead to AVN and the formation of thromboses in the femoral head? The goal in the near future would be to identify patients susceptible to AVN prior to thrombotic event and necrosis of the femoral head.

How Do We Get There?

Genetic testing of the general population is becoming more accessible every year. If we can create large databases based on these tests, we can eventually determine the genetic predisposition for AVN, and hopefully modify the gene in order to prevent the occurrence of AVN.

The gene expressions of OPG, RANK, and RANKL play an important role in the development of AVN of the femoral head, as well as in the progression of bone remodeling in the necrotic area [21]. A promising drug targeting this system is denosumab, which is a monoclonal antibody against RANKL. However, whether the long-term inhibition of RANKL has adverse effects remains to be elucidated, and will require future animal and clinical trials.

While we are investigating new techniques, surgeons should agree that when a collapse occurs, the patient should be referred for resurfacing or total hip replacement because any other treatment at present time will detrimentally affect the patient's quality of life.

References

1. Calori GM, Mazza E, Colombo A, Mazzola S, Colombo M. Core decompression and biotechnologies in the treatment of avascular necrosis of the femoral head. *EFORT Open Rev.* 2017;2:41–50.

CORR Insights

2. Cui Y, Kaisaierjiang A, Cao P, Wu ZY, Lv Q. Association of apolipoprotein A5 genetic polymorphisms with steroid-induced osteonecrosis of femoral head in a Chinese Han population. *Diagn Pathol.* 2014;9:229.
3. Fang T, Zhang EW, Sailes FC, McGuire RA, Lineaweaver WC, Zhang F. Vascularized fibular grafts in patients with avascular necrosis of femoral head: A systematic review and meta-analysis. *Arch Orthop Trauma Surg.* 2013;133:1–10.
4. Ficat RP. Idiopathic bone necrosi of the femoral head. Early diagnosis and treatment. *J Bone Joint Surg Br.* 1985;67:3–9.
5. Hungerford DS. Response: The role of core decompression in the treatment of ischemic necrosis of the femoral head. *Arthritis Rheum.* 1989;32:801–806.
6. Kim SY, Kim YG, Kim PT, Ihn JC, Cho BC, Koo KH. Vascularized compared with nonvascularized fibular grafts for large osteonecrotic lesions of the femoral head. *J Bone Joint Surg Am.* 2005;87:2012–2018.
7. Koo KH, Kim R, Ko GH, Song HR, Jeong ST, Cho SH. Preventing collapse in early osteonecrosis of the femoral head: A randomized clinical trial of core decompression. *J Bone Joint Surg Br.* 1995;77:870–874.
8. Lau RL, Perruccio AV, Evans HM, Mahomed SR, Mahomed NN, Gandhi R. Stem cell therapy for the treatment of early stage avascular necrosis of the femoral head: A systematic review. *BMC Musculoskelet Disord.* 2014;15:156.
9. Lieberman JR, Conduah A, Urist MR. Treatment of osteonecrosis of the femoral head with core decompression and human bone morphogenetic protein. *Clin Orthop Relat Res.* 2004;429:139–145.
10. Liu B, Cao Y, Wang D, Yao G, Bi Z. Vascular endothelial growth factor -634G/C polymorphism associated with osteonecrosis of the femoral head in a Chinese population. *Genet Test Mol Biomarkers.* 2012;16:739–743.
11. Mao Q, Wang W, Xu T, Zhang S, Xiao L, Chen D, Jin H, Tong P. Combination treatment of biomechanical support and targeted intra-arterial infusion of peripheral blood stem cells mobilized by granulocyte-colony stimulating factor for the osteonecrosis of the femoral head: A randomized controlled clinical trial. *J Bone Miner Res.* 2015;30:647–656.
12. Papakostidis C, Tosounidis TH, Jones E, Giannoudis PV. The role of "cell therapy" in osteonecrosis of the femoral head. *Acta Orthop.* 2016;87:72–78.
13. Plakseychuk AY, Kim SY, Park BC, Varitimidis SE, Rubash HE, Sotereanos DG. Vascularized compared with nonvascularized fibular grafting for the treatment of osteonecrosis of the femoral head. *J Bone Joint Surg Am.* 2003;85:589–596.
14. Sadile F, Bernasconi A, Russo S, Maffulli N. Core decompression versus other joint preserving treatments for osteonecrosis of the femoral head: A meta-analysis. *Br Med Bull.* 2016;118:33–49.
15. Sen RK, Tripathy SK, Aggarwal S, Marwaha N, Sharma RR, Khandelwal N. Early results of core decompression and autologous bone marrow mononuclear cells instillation in femoral head osteonecrosis: A randomized control study. *J Arthroplasty.* 2012;27:679–686.
16. Shah SN, Kapoor CS, Jhaveri MR, Golwala PP, Patel S. Analysis of outcome of avascular necrosis of femoral head treated by core decompression and bone grafting. *J Clin Orthop Trauma.* 2015;6:160–166.
17. Smith SW, Fehring TK, Griffin WL, Beaver WB. Core decompression of the osteonecrotic femoral head. *J Bone Joint Surg Am.* 1995;77:674–680.
18. Sotereanos DG, Plakseychuk AY, Rubash HE. Free vascularized fibula grafting for the treatment of osteonecrosis of the femoral head. *Clin Orthop Relat Res.* 1997;344:243–256.
19. Urbaniak JR, Coogan PG, Gunneson EB, Nunley JA. Treatment of osteonecrosis of the femoral head with free vascularized fibular grafting. A long-term follow-up study of one hundred and three hips. *J Bone Joint Surg Am.* 1995;77A:681–694.
20. Wang XY, Niu XH, Chen WH, Lin N, Song JN, Chen B, Jin H. Effects of apolipoprotein A1 and B gene polymorphism on avascular necrosis of the femoral head in Chinese population. *Zhongguo Gu Shang.* 2008;21:99–102.
21. Xiong MY, Li-Qiang L, Shi-Qiong L, Zhen-Hui L, Hang-Fei G. Effects of osteoprotegerin, RANK and

CORR Insights

RANKL on bone destruction and collapse in avascular necrosis femoral head. *Am J Transl Res.* 2016;8:3133–3140.

22. Zhao D, Cui D, Wang B, Tian F, Guo L, Yang L, Liu B, Yu X. Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. *Bone*. 2012;50:325–330.