closer examination, we agree that the investigation by Sun et al.[1] warranted inclusion and may have been inadvertently excluded because of the use of irradiated allografts. Additionally, the effect of duplicate publication bias must be acknowledged in comparative studies with updated follow-up.[2,3] Although negative results are underemphasized in the current literature, the selected studies in our review largely indicate a lack of statistically significant differences between autograft and nonirradiated, nonchemically treated allografts on specific clinical end points. Interestingly, Mariscalco et al.[4] recently performed a similar systematic review and also failed to demonstrate any significant differences in graft failure rate, laxity measures, patient-reported outcome scores, or combinations of these factors.

Heterogeneity was also assessed in the current study but not featured in the final publication. Similarly, the authors agree sensitivity analysis offers meaningful information in selected studies, and this methodology has been used in our previous publications evaluating outcomes after anterior cruciate ligament reconstruction.[5,6]

Again, the authors would like to thank you for your interest in our work.

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Mesenchymal Stem Cells Versus Fat Pad–Derived Cells

To the Editor:

We read the article "Mesenchymal Stem Cell Injections Improve Symptoms of Knee Osteoarthritis" in the April 2013 issue of your highly acclaimed journal with great interest.[1] We congratulate Koh et al. for their work, but we are very concerned about the erroneous use of the term "fat pad–derived mesenchymal stem cells (MSCs)" instead of "fat pad aspirate concentrate" or "fat pad–derived cells" (probably containing a small number of mesenchymal stem cells) in the article. It leads to serious confusion for the readers including ourselves.

To use the term "fat pad–derived MSCs," the cells should have been isolated from human adipose tissue by culture expansion and then characterized by the following: self-renewal, expression of specific cell surface markers, and multilineage differentiation. Thus the obtained cell population is relatively homogeneous,[2] which can be designated as "MSCs." The other term, "fat pad aspirate concentrate" or "fat pad–derived cells," means that the cell population is not isolated by culture expansion, so the cells are heterogeneous and may contain only a small number of MSCs.[2]

In the introduction to the article, Koh et al.[1] state that "Buda et al. advocated the use of a one-step technique in repairing osteochondral lesions of the knee with bone marrow–derived mesenchymal stem cell transplantation." However, the cells used in the study by Buda et al.[3] were not "MSCs" but were "bone marrow–derived cells" (in other words, "bone marrow aspirate concentrate"). It is clear that the title of the article only used the term "bone marrow–derived cells." We believe that it is a serious error to interchange the term "bone marrow–derived cells" with "bone marrow–derived MSCs" because it is well known that both entities are different from each other, and this error adds more confusion to the already confusing information in terms of the clinical results of various types of cell therapies.

Moreover, in the paragraph describing the surgical procedure and MSC harvesting technique, Koh et al.[1] described that "MSCs were derived and counted with a hemocytometer, as described previously."[4,5] However, in the referenced articles,[4,5] cells from the infrapatellar fat pad were cultured and expanded in MSC

expansion media. In this study cells from the infrapatellar fat pad were not cultured; thus the cell preparation took only 3 to 4 hours. Isolation of MSCs by culture expansion needs at least several days. Thus the authors' method for cell preparation was completely different from the previous method of MSC preparation in the referenced articles.[4,5] This is a serious error in the description of the methods and citing of references.

Although we acknowledge that this article is a leading clinical study using "fat pad–derived cells" in arthritic patients, we believe that it is very important to understand that the results of this study are not the results of using MSCs. We would like to ask the authors to change the erroneous term "mesenchymal stem cells" used in their article to an appropriate term—"fat pad-derived cells" or "fat pad aspirate concentrate." We look forward to their response to our concerns.

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Note: The authors report that they have no conflicts of interest in the authorship and publication of this letter.

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Authors' Reply

We appreciate the interesting and perceptive comments by Ha and Park regarding our recent study. The review's primary concern is the terms "fat pad–derived mesenchymal stem cells (MSCs)" and "fat pad aspirate concentrate" or "fat pad–derived cells." To use the term MSCs, the cells should possess the following characteristics: self-renewal, the expression of specific cell surface markers, and the capacity for multilineage differentiation. In the "Methods" section of our article, we briefly described the sample collection method and MSC isolation technique. According to the article, after centrifugation, the resulting samples were definitely "fat pad aspirate concentrates" or the "stromal vascular fraction."[1] Although we actually performed, however, the entire process as described by Zuk et al.,[1] we did not include it in this article and abbreviated on purpose the above process of the methodology describing the identification of MSCs from the stromal vascular fraction (SVF). Therefore, to enhance the clarity for the readers, we have described herein the entire MSC identification process with the subsequent results.

Isolation of SVF and MSCs From Subcutaneous Adipose Tissue. In the operating room, the infrapatellar fat pad was collected (mean weight, 9.1 g; range, 6.4 to 13.1 g), suspended in phosphate-buffered saline solution (PBS), placed in a sterile box, and transported to a laboratory. Mature adipocytes and connective tissues were separated from the SVF by centrifugation, as reported by Zuk et al.[1] The parts of the SVF were subjected to laboratory analysis to examine the plastic-adherent cells that form colony-forming units—fibroblasts (CFU-F) and confirm the multilineage differentiation of adipose-derived stem cells.

Assessment of Plastic-Adherent Cells That Form CFU-F and Immunophenotyping of Adipose-Derived Stem Cells. To evaluate the frequency of mesenchymal-like progenitors in patients' SVF, cells were cultured in T25 flasks at a final concentration of 16 cells/cm^2. Colonies consisting of greater than 50-cell aggregates were scored under an optical microscope, and the immunophenotype of adipose-derived stem cells was analyzed by flow cytometry (FACS). MSC marker phenotyping was performed as previously described.[2]

Confirmation of Multilineage Differentiation of Adipose-Derived Stem Cells. Adipose-derived stem cells were plated at 2×10^3 cells/cm^2 in DMEM containing 10% FBS and allowed to adhere for 24 hours. The culture medium was then replaced with specific inductive media to determine the adipogenic, osteogenic, and chondrogenic differentiation potential, as previously reported.[2]

Cell Isolation and Characterization of Adipose-Derived Stem Cells. We evaluated the capacity of human subcutaneous adipose tissue to generate mesenchymal progenitors using the CFU-F. Thus, after isolation, adipose-derived stem cells represented a mean of 10.1% of SVF cells (range, 7.1% to 12.2% of SVF cells). After the SVF was isolated, a mean of 1.18×10^6 stem cells (10.1% of 1.19×10^7 SVF cells) were prepared. FACS characterization indicated positive expression of the surface markers CD90 (98.4%) and CD105 (94.5%) and negative expression of CD34 (8.1%) and CD14 (3.6%), as shown previously in another article.[1] Adipose-