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Measured Level of Human Adipose Tissue–Derived Stem Cells in Adipose Tissue Is Strongly Dependent on Harvesting Method and Stem Cell Isolation Technique

Sir:

We have read with great interest the study entitled “Measured Level of Human Adipose Tissue–Derived Stem Cells in Adipose Tissue Is Strongly Dependent on Harvesting Method and Stem Cell Isolation Technique.”¹ In the article, Alstrup et al. aim to compare the characteristics of adipose-derived mesenchymal stromal cells isolated from two types of plastic surgery samples, pieces of dermolipectomies that correspond to excised tissues, and lipoaspiration using the Coleman technique. We would like to thank the authors for this study because it is really important information to establish which method of harvesting is best.

Although this is not the first study comparing these two harvesting techniques, the authors have been able to overcome shortcomings of past studies.^{2,3} However, important points should be clarified after reading this article.

First, the authors do not specify where liposuction was performed. Indeed, if liposuction is performed at the subumbilical level (either before or after abdominoplasty), as is often the case, the repeated back-and-forth movements and tunnels left after liposuction make it impossible to know whether the excised tissues remain intact, as the authors claim, making an accurate comparison impossible. If it is another body region that is lipoaspirated, it is important to specify this because there are variations in cell yields depending on the body regions, as Alstrup et al. rightly point out in the Introduction.⁴ This point may represent a major bias of the study.

Second, the main data of this study show that enzymatic digestion associated with mechanical distortion results in 1.8 times more adipose-derived mesenchymal stromal cells in the excised tissue than in liposuction, highlighting the advantage of their combined digestion technique and the interest of using an intact tissue. In addition, the authors show that this difference is no longer significant with enzymatic digestion alone.

We agree with the authors that liposuction is too selective and does not recover vessels or fibrous tissue where adipose-derived mesenchymal stromal cells are present in high quantities. We would simply like to add that liposuction is more hemorrhagic than a scalp excision, and therefore much of the aspirated tissue contains blood without adipose-derived mesenchymal stromal cells. Unfortunately, the authors do not discuss the results comparing the two techniques of sampling with enzyme digestion alone. However, Table 2 shows that there is a higher number of cells in the liposuction (33 versus 25), which is in disagreement with the results of their combined digestion. Enzyme digestion alone still represents the gold standard, so in the end, liposuction would seem to be more effective than

excised tissue. This inconsistency showed that mechanical digestion was necessary for collagenase to correctly digest excised tissues. It seems wise to now compare enzymatic digestion to mechanical digestion alone, which is increasingly practiced in studies and is producing interesting results. Moreover, because the data presented here are very different from the other publications on excised tissues,^{2,3} additional studies will be necessary to know the true potential of abdominoplasties as a donor site.

Other pitfalls should also be noted here. The authors talk about adipogenic and osteogenic differentiation but do not present any numerical data. Polymerase chain reaction experiments are essential to know the true power of differentiation. In addition, tests on angiogenic capacities and on immunomodulation (major capacity of adipose-derived mesenchymal stromal cells in regenerative medicine) would have been appreciated. In conclusion, we would like to thank Alstrup and his team for this innovative work, which offers new possibilities in the use of adipose-derived mesenchymal stromal cells.

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DISCLOSURE

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Reply: Measured Level of Human Adipose Tissue-Derived Stem Cells in Adipose Tissue Is Strongly Dependent on Harvesting Method and Stem Cell Isolation Technique

Sir:

We would like to thank the authors of the letter for very relevant questions regarding our article and a chance to clarify the topics.¹ For the first question, abdominoplasty was performed and the infraumbilical tissue was excised. Subsequently, the abdominal skin was split. Then, the tissue sample was split into two halves: liposuction was performed on one half of the tissue sample and excision was performed on the other half. Thus, liposuction and excision were performed at identical anatomical entities, and no manipulation of excised adipose tissue samples occurred before the stem cell isolation procedure.

As for the second question regarding adipose tissue-derived mesenchymal stem cell yields, the authors of the letter state that the combination of mechanical distortion and enzymatic digestion increase adipose tissue-derived stem cell yield of a factor of 1.8 between excised and aspirated adipose

tissue samples. This statement is not clear to us. Table 1 describes the relations between the investigated groups; we report a factor of 2.1 for flow cytometry and 1.6 for fibroblast colony-forming unit assay quantification between excised and aspirated adipose tissue samples when isolated with the combination of mechanical distortion and enzymatic digestion. A factor of 1.8, quantified by fibroblast colony-forming unit assay, was found when we compared standard enzymatic digestion and combination of mechanical distortion and enzymatic digestion for aspirated adipose tissue. A factor of 2.3 was reported when quantified using flow cytometry.

A follow-up notion, that liposuction is a more hemorrhagic than excision, and that the liposuction samples therefore can be diluted with blood (not containing adipose tissue-derived mesenchymal stem cells) is mentioned. As we performed liposuction after abdominoplasty, the blood supply was disconnected, minimizing the risk of dilution noted by the authors of the letter. We do not have any data regarding this concern, but we did not notice a large dilution when the samples were washed before enzymatic and mechanical isolation.

As for discussing the results comparing excised and adipose tissue samples using standard enzymatic digestion, these data can be found in Table 1 with a median ratio of 0.94 and a value of $p = 0.72$. This finding is a main conclusion of the study, highlighting that standard enzymatic isolation is insufficient in extracting all resident adipose tissue-derived mesenchymal stem cells. We have tried to highlight this in the second sentence in the Discussion section and through comparison to existing literature.

The authors of the letter mention that Table 2 reports a higher number of cells in the aspirated samples compared to excised samples (33,000 adipose-derived stem cells/ml versus 25,000 adipose-derived stem cells/ml quantified by flow cytometry) when only standard enzymatic isolation is performed. The authors of the letter further mention that this contradicts the conclusions of combination of enzymatic digestion and mechanical distortion.

As Table 2 demonstrates the average yields for each group, we recommend the reader to check Table 1 for statistical comparison between groups. In Table 1, comparison between excised and aspirated yield from standalone enzymatic digestion is presented with a median ratio of 0.94 and a value of $p = 0.72$; thus, the difference is far from statically significant and therefore does not contradict the conclusion of combination of enzymatic digestion and mechanical distortion.

It should be noted that the comparison displayed in Table 1 is available only for the units adipose-derived stem cells per gram. However, comparison between the groups using adipose-derived stem cells per milliliter produced equal confidence intervals and p values. The unit of adipose-derived stem cells per gram was chosen, as this is a more