Dear Editor,

We thank the reviewers and editorial team for taking their efforts to improve the article to increase its value for publication. Herewith we submit the revised version of the article addressing the reviewer's comments and the action taken for their valuable suggestions have been mentioned below.

Reviewer 1 Comments	Authors Reply	Action Taken
1. This manuscript reviews the potential applications of therapeutic products containing adipose tissue-derived mesenchymal stem cells (ADSCs) at clinical settings. The authors first provide an overview of adipose tissue biology. Characterization and immunomodulation ability of ADSCs are then discussed. The authors subsequently review the potential applications of adipose tissue and its derivatives at clinical settings. This manuscript is interesting.	Thanks for the supportive comment.	None
2. There are many existing reviews on ADSCs. The authors should discuss the importance of this review in the last paragraph of introduction	Thanks for the comment. Aim of this review has been added as suggested.	Page No 4 Line No 25-27
3. ADSCs are also known to undergo multilineage differentiation and secrete bioactive factors and exosomes for promoting tissue repair and regeneration. These aspects should be briefly discussed before section "Derivatives and applications of adipose tissue".	Thanks for the comment. Mechanism of action of ADSC has been added as suggested before the "Derivatives and applications" section.	Page No 9 Line No 12-16
4. The authors should discuss the challenges of using ADSCs directly in clinical applications. Does transplantation of adipose	Thanks for the insightful comment. The challenges in the therapy and its future has been discussed as suggested.	Page No 22 Line No 17-26

tissues containing ADSCs or administration of ADSC-derived exosomes overcome such challenges?		
5. How does microfat grafting enhance therapeutic efficacy of ADSCs?	Thanks for the comment. Apart from being an adipogenic derivative with AD-MSC, the microfat showed retains the intact 3-dimensional architecture of adipose tissue. The mature adipocytes and SVF cells, fibrous scaffolds, and capillary fragments were well preserved. Compared with the nanofat and SVF-gel, the microfat could accommodate the natural environment for the survival of mature adipocytes and provide a natural niche for SVF cells to ensure optimal tissue regeneration. These advantages have been highlighted in the revised manuscript.	Page No 14 Line No 1-3
6. How does nanofat grafting improve therapeutic efficacy of ADSCs?	Thanks for the comment. Apart from being an adipogenic derivative with AD-MSC, the proportion of AD-MSC in the nanofat is higher than that in the microfat. The differences may be attributable to the method of preparation of the micro-fat where the fibers and their accompanying capillaries, which were the location of AD-MSCs were removed. In contrast, the ASCs were mechanically separated from the native site and concentrated in the nanofat thereby making them effective in terms of the number of AD-MSCs delivered to the target site. These advantages have been highlighted in the revised manuscript.	Page No 14 Line No 23-29
7. Do microvascular fragments (MVF) contain any ADSCs? This section should be removed if MVF do not contain ADSCs.	Thanks for the insightful comment. We have added content to the revised manuscript that explains the native biology of the MVF that MVFs contain stem cells antigen (Sca)-1/ VEGFR-2-positive endothelial progenitor cells and mesenchymal stem cells expressing common markers, such as CD44, CD73, CD90, and CD117. It was initially speculated that the high vascularization potential of MVFs is	Page No 16 Line No 14-17

	mainly due to these stem cell populations. When McDaniel et al. compared the regenerative properties of conventionally isolated adipose-derived stem cells and multipotent cells derived from an explant culture of microvascular fragments. They found that the latter ones exhibit a higher proliferation rate, an increased expression of genes involved in differentiation, and an improved ability to form capillary-like structures. In line with the concept of the 'stem cell niche', these findings indicate that compared to single cell isolates, microvascular fragments with the stem cell components within provides a more physiological environment maximizing their regenerative activity.	
8. How does transplantation of stromal vascular fraction (SVF) increase therapeutic efficacy of ADSCs?	In case of fat grafting, clinicians are challenged by the fat graft rejection with reported resorption rate ranging from 25-80% which is mostly due to the mature adipocyte undergoing apoptosis. When the lipoaspirate was given along with SVF, 35% greater graft retention was noted. Further, more prominent microvasculature was noted compared to the normal graft tissue suggesting its clinical potential. Hence, the therapeutic efficiency of the AD-MSC in the fat grafting techniques could be increased by using them along with SVF which act as a nourishing medium. Moreover in situations such as osteoarthritis where a ultrafiltrate fraction of adipose derivative such as SVF would be the ideal medium of choice to tap the benefits of AD-MSCs in cartilage regeneration. Revised manuscript has been added with this differential benefits.	Page No 19 Line No 16-23
9. The following relevant works should be cited and discussed. - Biosafety and bioefficacy assessment of human mesenchymal stem	Thanks for the insightful comment. The suggested works have been discussed and cited appropriately.	References 98,246

cells: what do we know so far (2019) Regenerative Medicine 13(2): 219-232. - Adipose-derived stem cells: current applications and future directions in the regeneration of multiple tissues (2020) Stem Cells International 2020: 8810813.		
Reviewer 2 Comments	**Authors Reply**	**Action Taken**
1. The manuscript describes the biology, characteristics, immunology, and clinical applications of adipose-derived products, mostly of which have recent evidence to support. The authors have provided the utility of various adipose derivatives helps in the improvisation of the existing regenerative therapies and their associated biomedical applications.	Thanks for the supportive comment.	None
2. I am a little confused about AD-MSCs and ADSCs. What are the differences of these two cells? The definition of "ADSCs" should be provided in the manuscript.	Thanks for the comment. The definition of "ADSC" has been provided to avoid unnecessary confusion in the terminology. Further we revised every place of use of AD-MSC with ADSC to maintain uniformity.	Page No 10 Line No 9,10
3. The authors mentioned in paragraph 3 of the "Introduction" section that "adipose tissue products in preclinical studies to promote the adipogenesis of stem cells". Is there any clinical trials or studies about the applications of adipose tissue products?	Thanks for the comment. So far only pre-clinical studies are available on the biomolecules and biodegradable three-dimensional scaffolds to interact with adipose tissue products in to promote adipogenesis.	References 14, 15
4. Is there any guideline or standard protocol on clinical applications of adipose derivatives?	Thanks for the comment. The expanding horizons of applications of ADSC utility needs guidelines and standardisation for universal application, which is the need of the hour. We could not find any guidelines on its applications rather we have the empirical FDA guidelines on the	None

	utility of stem cell for therapeutics which has also been highlighted in the manuscript.	
5. The subsections of section "Derivatives and applications of adipose tissue" are in general very brief. Please give more details or examples of their clinical applications.	Thanks for the comment. Detailed examples on every clinical applications have been added as suggested.	Page No 12 Line No 4-28 Page No 14 Line No 3-6 Page No 15 Line No 7-30 Page No 16 Line No 1-7 Page No 17 Line No 4-8 Page No 18 Line No 21-31 Page No 19 Line No 1-23 Page No 20 Line No 11-31 Page No 21 Line No 1-12
6. The authors mentioned in the section Adipose tissue biology, paragraph 1, that "the two types of adipose tissue defined are the white adipose tissue found in adults and the brown adipose tissue found in newborns". What is the difference between these two types of adipose tissue?	Thanks for the comment. white adipose tissue stores excess calories, and brown adipose tissue consumes fuel for thermogenesis using tissue-specific uncoupling protein 1 (UCP1)[1, 2]. BAT was once thought to have a functional role only in rodents and human infants, but it has been recently shown that in response to mild cold exposure, adult human BAT consumes more glucose per gram than any other tissue[3]. In addition to this non-shivering thermogenesis, human BAT may also combat weight gain by becoming more active in the setting of increased whole-body energy intake[4-5]. 1. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev. 2004; 84:277–359.	None

	2. Richard D, Picard F. Brown fat biology and thermogenesis. Front Biosci. 2011; 16:1233–1260. 3. Orava J, et al. Different metabolic responses of human brown adipose tissue to activation by cold and insulin. Cell Metab. 2011; 14:272–279. 4. Wijers SL, Saris WH, Marken Lichtenbelt WD. Individual thermogenic responses to mild cold and overfeeding are closely related. J Clin Endocrinol Metab. 2007; 92:4299–4305. 5. van Marken Lichtenbelt WD, et al. Cold-activated brown adipose tissue in healthy men. N Engl J Med. 2009; 360:1500–1508.	
7. Some columns of Figure 1 are missing, such as vascular fragment. Also, CD4 cells are showed in Figure 1 but not mentioned in section "Adipose tissue biology", paragraph 2, why?	Thanks for the comment. Figure 1 has been revised. Statement on CD4 cells has been added in the biology section.	Figure 1 Page No 6 Page No 5 Line No 16-17
8. What is "HSCs" in section "Characterization of ADSCs", paragraph 3?	Thanks for the keen observation. It's a typo. It has been amended appropriately to MSC.	Page No 8 Line No 5
9. Textual: The last sentence in section "Characterization of ADSCs", paragraph 3, "CD34+ and CD34- pericytes sto be the identity of…".	Thanks for the comment. Statement has been ameded.	Page No 8 Line No 10