March 4, 2017

Dear Editors,

Thank you for your comments on the manuscript, No 32790, Clinical application of concentrated bone marrow aspirate in orthopaedics: a systematic review. The authors have addressed the edits and have corrected these within the body of the text and have attached our reviewer response below. We believe this manuscript will make a significant contribution to the understanding of the current literature on the use of concentrated bone marrow aspirate in the field of orthopedics. We hope this manuscript will promote further research on this topic. Many thanks for the opportunity to publish this manuscript in World Journal of Orthopedics.

Sincerely,

Arianna Gianakos

COMMENTS TO AUTHORS

The paper is well written,well structured in introducing the potential benefits of utilizing cBMA in the clinical setting. However，it would be helpful to discuss the potential molecular mechanisms of cBMA in enhancing tissue regeneration .

AUTHOR RESPONSE:

Thank you for your comments. We have included a short section on the mechanism of cBMA in tissue regeneration and have included this below.

Summary of MSC Mechanism

Adult BMSCs have two primary functions: (1) to differentiate into distinctive end-stage cell types such as bone, cartilage, and tendon; (2) to secrete bioactive macromolecules that are both immunoregulatory and regenerative.[44] Every cell has a half-life with a turnover sequence mechanism that gives rise to the phenotypes in complex tissues. This allows for both replacement of cells, as well as, the capacity for differentiation into bone, cartilage, and tendon. BMSCs also have characteristic markers of pericytes, which are smooth muscle vascular support cells that may play an important role in stem cell differentiation.[44,45] MSCs also demonstrate trophic activity through secretion of both cytokines and growth factors.[46] The intrinsic secretory activity of MSCs affords a regenerative environment for the repair of injured or damaged tissues.[44] Tissue-specific scaffolds have also been utilized in tissue engineering to reform tissues when MSCs are implanted into different tissue sites. The capacity for cell regeneration and repair relies on several additional factors including patient age, extent of

injury/damage, and the functional ability of MSCs to grow and repair. Tissue engineering allows for the manipulation of both the delivery of MSCs to targeted tissue sites and the microenviroment for which cells grow in order to enhance differentiation.[44] Future investigations will continue to focus on harnessing the therapeutic potential of MSCs in tissue specific environments to enhance regeneration and repair of cartilage, bone, and tendon.