Reviewer's report

Title: Comparison of endothelial progenitor cell function in type 2 diabetes with good and poor glycemic control

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Reviewer: Jaw-Wen Chen

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There still many issues that remain unclear even after revision.

1) In table 1, please add the number of patients receiving OHA and/or insulin for blood sugar control. Given the significant different in blood sugar control between the 2 groups, it is obviously that the DM medications were also different between the groups. This is very important since OHA and insulin themselves (not only PPARg agonists) may potentially modify the EPC function. Besides, a significant portion of the DM patients received statins. It is well documented that statins may improve EPC function. Please also discuss this issue.

2) In figure 1g, the number of CD34+/VEGFR-2- cells seem significantly less in DM than in normal subjects. Please clarify and show the p value.

3) In figure 2-a, the presence of red and green color is different in figure a3 and in figure a4. Please use arrows to clearly indicate the presence of red or green color on the figures. Please identify in figure legends that figure 2 b and c only present the data from DM patients. However, unless there is something wrong, the data from normal subjects should be also present for comparison.

4) About figure 3 c and d, the response to reviewers' comments is not acceptable. Even if there were no statistically difference between the proliferation "inhibition" (not "capacity" as that indicated in the figure legend) of EPCs from normal subjects and that from DM patients, it is still not reasonable while the baseline EPC number was significantly less in DM patients than in normal subjects. According to the authors reply, it seems that EPCs from DM patients may have normal proliferation. Please discuss and explain the above issue.

5) In figure 4, the glucose-induced apoptosis is increased in EPCs from DM patients than that from normal controls. However, there is no difference(?) in cell proliferation between these EPCs from different origins. Please explain why and how.

6) In page 13, it is indicated that "Apoptotic bodies from injured endothelium, act as angiogenic factors, can induce the differentiation of circulating EPCs toward mature endothelial cells which are used to repair the damaged vessel, thus reducing the number of circulating EPCs [30]." However, in reference 30, it was indicated that the apoptotic bodies may stimulate and increased the number of EPCs. Please clarify this issue.

7) In page 14, it is indicated that "The mechanism contributing to the reduction of
circulating EPCs in diabetes is unknown, it may be due to decreased proliferation and/or accelerated cell death. Previous studies showed an accumulation of EPCs in resting stage and decreased number of EPCs in proliferative stage after exposure to hyperglycemic condition [35]." However, according to the authors' reply and data of this study, there is no decreased proliferation of the EPCs from DM patients. The discussion should then focus on why there is no change in proliferation of EPCs in this study. Furthermore, it is even more important to discuss why there is increased apoptosis of these EPCs after exposure to hyperglycemic condition.

8) In page 15, it is indicated that "However, the observed circulating EPC number in patients with good glycemic control did not reach the level found in healthy controls. This might arise from several mechanisms including long-lasting hyperglycemic-induced EPC damage and increasing use of circulating EPCs in revascularization of diabetes-associated atherosclerotic vessels." The above is mainly an speculation. There is no any evidence in this study that DM patients with good glycemic control may have to revascularize diabetes-associated atherosclerotic vessels. Please omit this part of discussion.

In general, this clinical study is purely observational. The current study design may not give any definite mechanistic insights. There are many confounding factors including the disease duration, the baseline glucose level, medication used, and the treatment duration may alter the EPC function. Only a prospective, randomized, interventional study with longitudinal follow-up could determine whether better glycemic control may improve EPC function better.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests'