Amendments based on comments from reviewer 1

We appreciate valuable comments. We took a significant amount time and effort to address reviewer's comments. It looks much better than previous version. We strongly believe that we successfully address the issues on a point-by-point basis for all comments. We also believe that we meet high standard of your journal. Thank you.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Generally, it is an interesting and nice review. I have following comments.

1. Be careful to interpret "Obesity increases the risk of T1DM" "Decreasing body fat helps to increase insulin sensitivity, particularly in T1DM ....."

→ Thank you for the comment. The contents of T1DM were deleted from the manuscript.

"Patients with T2DM do not release enough insulin to control glucose due to loss of cells, deterioration of their function, or both[23]. Obesity increases the risk of T2DM[24, 25] partly by decreasing insulin sensitivity, i.e., insulin does not cause a normal reduction in blood glucose."

"Decreasing body fat helps to increase insulin sensitivity, particularly in T2DM patients, because there is a positive association between body fat, peripheral insulin-resistance, and pro-inflammatory conditions[70]."

2. NAFLD/MAFLD is highly prevalent in type 2 diabetes, and live cell is very sensitive to hypoxia, so how about the hypoxia therapy in diabetic patients with NAFLD/MAFLD?

→ Thank you for the suggestions. In an attempt to understand obesity-induced changes in liver oxygen homeostasis, a previous study reported that liver HIF-1α expression was increased mainly by soluble factors released from obese adipocytes, leading to decreased incretin effects. Also, deletion of hepatocyte HIF-1α protected obesity-induced glucose intolerance without changes in body weight, liver steatosis, or insulin resistance. Mechanism studies related to hypoxia and liver cells are underway in animals. If these mechanisms are based on ensuring safety, hypoxia therapy will be used effectively in diabetic patients with NAFLD/MAFLD.

"Lee YS, Riopel M, Cabrales P, Bandyopadhyay GK. Hepatocyte-specific HIF-1α ablation improves obesity-induced glucose intolerance by reducing first-pass GLP-1 degradation. Sci Adv. 2019 Jul 3;5(7):eaaw4176. doi: 10.1126/sciadv.aaw4176. PMID: 31281892; PMCID: PMC6609217."

3. The extent of hypoxia and duration is very important, so not so many clinical studies about this and more attention should be paid to interpret.

→ Thank you for the advice. Various studies have been conducted on the effect of hypoxic exposure in a healthy adult. However, the duration for hypoxic exposure was not defined accurately in patients with T2DM, adding the section "Possible health risks of exercise intervention under the hypoxic condition on T2DM". In conclusion, the following potential benefits and safety points were suggested:

"Future studies should evaluate the potential benefits of exposure to hypoxic conditions during exercise, to design new intervention methods (normobaric hypoxia vs. hypobaric hypoxia or hyperbaric hypoxia) for treating T2DM patients. Overall, exposure to hypoxic conditions during exercise in T2DM patients have the potential value of adaptation to stress stimulation in terms of clinical treatment, which can protect against pathological biology and other stresses in diabetes. Overall, the literature suggests that exposure to hypoxic conditions during exercise (simulated altitude of ca. 3000 m) is highly likely to improve the health condition of patients with diabetes. However, there is insufficient evidence for the safety of exposure to short-term hypoxic conditions during exercise in T2DM patients, and further research is needed to develop suitable interventions. Thus, exposure to hypoxic conditions during exercise should be performed with consideration of safety precautions, and patients should be advised by a medical doctor before undertaking exposure to hypoxic conditions."

4. Do those ordinary persons from high altitudes have a lower incidence of diabetes compared to those from sea level?

→ Thank you for the comment. The previous study has found an inverse association between altitude and diabetes. Male living at high altitudes (between 1,500 and 3,500 meters) have been shown to have a lower prevalence of diabetes than those at lower altitudes (below 500 meters). However, diabetes requires a careful approach because it is highly influenced by energy intake and lifestyle.

"Woolcott OO, Castillo OA, Gutierrez C, Elashoff RM, Stefanovski D, Bergman RN. Inverse association between diabetes and altitude: a cross-sectional study in the adult population of the United States. Obesity (Silver Spring). 2014 Sep;22(9):2080-90. doi: 10.1002/oby.20800. Epub 2014 May 28. PMID: 24890677; PMCID: PMC4149588."