Dear Editor and Reviewers:

Thank you for your letter and the reviewers' comments concerning our manuscript entitled "Targeting Epicardial Adipose Tissue: A Potential Therapeutic Strategy for Heart Failure with Preserved Ejection Fraction with Type 2 Diabetes Mellitus " (ID: 82803). Those comments are valuable and helpful for revising and improving our paper. We have studied comments carefully and have made corrections which we hope meet with approval. Revised portions are marked in red on the paper. The main corrections in the paper and the response to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

**Reviewer #1**: It is a well-design study adding new information to the literature. According to my knowledge, it is a novel paper in its field opening new horizons for further evidence. Authors, succeed to present their findings in a clear way. In addition, the object as well as the results are appropriately discussed in the context of previous literature explaining the importance of the manuscript in its field. Authors succeed to present their data in a clear way adding information to the existing literature. Therefore, I have no corrections or further work to propose for the improvement of the manuscript and therefore it can be published unaltered.

**Response:** We gratefully thank for the precious time the reviewer spent making the important comment. We have extensively modified our manuscript according to the associate editor and reviewers' comments, but they do not affect the overall content and structure of the article. Thank you again for your positive comments.

**Reviewer #2**: There are two important reviews in the same field: 1. van Woerden G, van Veldhuisen DJ, Westenbrink BD, de Boer RA, Rienstra M, Gorter TM. Connecting epicardial adipose tissue and heart failure with preserved ejection fraction: mechanisms, management and modern perspectives. Eur J Heart Fail. 2022 Dec;24(12):2238-2250. doi: 10.1002/ejhf.2741. 2. Packer M, Lam CSP, Lund LH, Maurer MS, Borlaug BA. Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: a hypothesis to explain influence of sex on the evolution and potential treatment of the disease. Eur J Heart Fail. 2020 Sep;22(9):1551-1567. doi: 10.1002/ejhf.1902. However, this manuscript includes type 2 diabetes mellitus on HFpEF and its association with

epicardial fat. There is a special interest on this field the last years. The authors have explained in detail all the principal aspects: The physiopathological mechanisms and the non and pharmacologycal therapeutic strategies.

**Response:** We sincerely thank the reviewer for careful reading. We have carefully read the relevant literature you provided. We tried our best to improve the manuscript and made some changes according to the associate literature. These changes will not influence the content and framework of the paper. Thank you again for your positive comments.

**Reviewer #3:**

**Q1.** The authors' writing of the current manuscript needs substantial improvement. Assistance from a native speaker or experienced academic writer is strongly encouraged.

**Response:** We were sorry for some of the language errors.Thank you for your reminder. We have carefully checked the full text and tried our best to polish the language in the revised manuscript under the guidance of an experienced academic writer. We hope it will meet the standard of the World Journal of Diabetes.

**Q2.** The authors may read the recent literature: Diabetic HFpEF: Benko, Jakub, et al. "Diabetic Heart Failure with Preserved Left Ventricular Ejection Fraction: Review of Current Pharmacotherapy." Journal of Diabetes Research 2022 (2022). McHugh, Kelly, et al. "Heart failure with preserved ejection fraction and diabetes: JACC state-of-the-art review." Journal of the American College of Cardiology 73.5 (2019): 602-611. Altara, Raffaele, et al. "Targeting obesity and diabetes to treat heart failure with preserved ejection fraction." Frontiers in endocrinology 8 (2017): 160. Abudureyimu, Miyesaier, et al. "Heart failure with preserved ejection fraction (HFpEF) in type 2 diabetes mellitus: from pathophysiology to therapeutics." Journal of Molecular Cell Biology (2022). Pop-Busui, Rodica, et al. "Heart failure: an underappreciated complication of diabetes. A consensus report of the American Diabetes Association." Diabetes Care 45.7 (2022): 1670-1690. EAT & Diabetic HFpEF: Elsanhoury, Ahmed, et al. "Epicardial Fat Expansion in Diabetic and Obese Patients with Heart Failure and Preserved Ejection Fraction—A Specific HFpEF Phenotype." Frontiers in Cardiovascular Medicine

(2021): 1031. Salvatore, Teresa, et al. "Dysregulated Epicardial Adipose Tissue as a Risk Factor and Potential Therapeutic Target of Heart Failure with Preserved Ejection Fraction in Diabetes." Biomolecules 12.2 (2022): 176. Iacobellis, G. Epicardial adipose tissue in contemporary cardiology. Nat Rev Cardiol 19, 593–606 (2022). https://doi.org/10.1038/s41569-022-00679-9.

**Response:** We deeply appreciate the reviewer's suggestion. We carefully read the above literature and made the necessary changes to the manuscript according to them. Thank you again for your valuable suggestions.

**Q3.**The comments of the current manuscript is listed as below.

Abstract: Line 5 Page 3: What is the definition of “Diabetic HFpEF” ? Is it interchangeable with “HFpEF with DM” Does it means the etiology of HFpEF is DM, or HFpEF with the presence of DM but not necessarily the etiology. Line 11 Page 2: “improving the dysfunction of EAT” does not make sense. “Dysfunction” cannot be “improved” Also, the author repeatedly mentioned “EAT dysfunction”, which is inappropriate, as the abnormality of EAT includes both aspects of function and structure. Line 16 Page 3- This sentence is vague. What is “beneficial” for “HFpEF”: symptom relief, slowing disease progression, reducing cardiac remodeling, or improving prognosis? Line 18 Page 3- “effectiveness” is incorrect. “Efficacy” should be used The author should consider adding the statement that treating EAT should be additive to the standardized treatment of HFpEF according to the guideline. Key word: 2 duplicate words for EAT. Line 5 Page 4: “Effective interventions remain a severe clinical challenge due to the complex pathophysiological underpinnings.” ---This sentence does not make sense. some words like “A lack of ” should be added before “Effective intervention”--- The same mistake appears in Line 8 Page 5 Core Tips: Line 8 Page 5: “dysfunction” refers to the functional aspect, which is hard to define as “expension”. “Abnormalities”, rather than “dysfunction”, is recommended. Line 19-22 Page 5: “Although no treatment is available specifically for EAT, lifestyle management, bariatric surgery, and pharmaceutical interventions related to anti-cytokines, anti-hyperlipidemia, and anti-hyperglycemia have been shown to reduce the inflammation response or accumulation of EAT.”--- The exact text appears in the abstract, core tips, and intro. This should be edited to improve readabilities 2.1 Anatomy of EAT Line 12 Page 6: “accompanies”---This is Vague, which should mean “surround and cover”. Line 17-19 Page 6: “Microscopically, EAT consists typically of adipocytes specialized in energy storage, but also includes inflammatory cells (mainly macrophages and mast cells), immune cells, stromovascular cells, and ganglia [13].”---This is the normal histology of EAT. In a normal

human being, EAT contains a small amount of inflammatory cells, but in a diseased condition, the aggregation of inflammatory cells and microvascular network expands.

The pathophysiology of EAT should also be mentioned here or with 2.3 Pathophysiology of EAT. 2.2 Pathology of EAT This whole section is about the physiology of EAT, but not about the pathology of EAT. Either the subtitle or the content needs to be changed. 2.3 Pathophysiology of EAT Line 15-19 Page 7: References are needed in these two sentences.

3.1 EAT in the pathophysiology of diabetic HFPEF Line 12-15 Page 8: References are needed in these two sentences. Para 2 Page 9: The interaction between EAT and DM should be discussed here. For example, DM may accelerate EAT deposition; EAT may increase local insulin resistance. Both the pro-inflammatory effect of EAT and DM may exhibit additive effects on the myocardium to worsen cardiac remodeling and coronary arteries to accelerate coronary atherosclerosis and decrease coronary blood supply, even when CAD is not the etiology of HFpEF.

3.2 Relationship between Increased EAT and Clinical Characteristics of HFpEF HFpEF not only refers to cardiac structure and mechanical function but also includes electrophysiology. Afib is common in patients with HFpEF. EAT is widely known to be closely associated with Afib (For example: Ernault, Auriane C., et al. "The Secretome of Atrial Epicardial Adipose Tissue Facilitates Reentrant Arrhythmias by Myocardial Remodeling." Heart Rhythm (2022).; Ernault, Auriane C., Veronique MF Meijborg, and Ruben Coronel. "Modulation of cardiac arrhythmogenesis by epicardial adipose tissue: JACC State-of-the-Art Review." Journal of the American College of Cardiology 78.17 (2021): 1730-1745.). This should be considered to be discussed. Additionally, any literature on histology & pathology between EAT and HF, as well as DM, is recommended to be incorporated, as this paragraph mainly discusses the relationship between EAT and HF according to imaging modalities, but no mechanistic association is unfolded.

4 Current Interventions Targeting EAT and Future Therapeutic Perspectives in HFpEF with T2DM Line 12 Page 10--- The author stated that “EAT acts as a critical contributor to the development and progression of diabetic HFpEF”. Using “critical” might outweigh the role of EAT too much. Currently, most evidence that EAT leads to HFpEF is based on epidemiology and imaging. Rarely there is any solid histological and pathological evidence confirming the role of EAT in HFpEF. The author needs to tone down the statement.

4.1 Non-pharmacological interventions Line 1 Page 11: “and an improvement in LV hypertrophy ”---

Not an improvement, should be an “alleviation” Line 1 Page 11: “5% reduction ”--- 5% difference in serial imaging assessment can be due to measurement variability. Especially EAT volume is difficult to measure at the apex. Be cautious of the statement or citing this reference. Line 22 Page 12: “EAT regression” means “reverse remodeling”?

4.2.3 Anti-hyperglycemic drugs Line 17 Page 13: “its positive effects on body weight and fat composition” --- It should be “positive effects on reducing body ---” Line 15-17 Page 14: “Therefore, considering the therapeutic effects of modulating PPAR-γ, targeting PPARγ remains a promising treatment approach and deserves the development of new and safer PPARγ-modulating drugs.”----- The therapeutic effect of targeting EAT to treat HFpEF might be cancelled out by PPAR-y. The author’s saying here needs to be more cautious and conservative.

5 Summary and Future Perspectives Line 7-8 Page 17: “T2DM is an essential driver of the occurrence and development of HFpEF “---This is incorrect. DM can be one of the essential driver, but some HFpEF patients do not have DM

**Response:** We appreciate the reviewers' attention to the flaws of our text. We have changed all the reviewers' suggestions. And here, we did not list the changes but marked them in red in the revised paper. We appreciate Editors/Reviewers’ warm work earnestly and hope that the correction will be approved.

We tried our best to improve the manuscript and make some changes. These changes will not influence the content and framework of the paper. And here, we did not list the changes but marked them in red in the revised paper.

We appreciate Editors/Reviewers' warm work earnestly and hope that the correction will be approved.

Once again, thank you very much for your comments and suggestions.

Yours sincerely,

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