Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Thank you for submitting excellent manuscript to this journal.

Answer: Thanks for your review and comments.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: In the present review by Wang et al., the authors summarized the existing evidence regarding the modification of immune system by obesity and its role in the progression of T2DM. Overall, it was an instructive review and editing of the paper by a native editor even can help to improve readability of the paper. Here are a few comments for the authors: - As you know, not only obesity but also distribution of body fat is involved in the pathophysiology of diabetes and central obesity or visceral or ectopic accumulation of body fat is more determinant risk factor than obesity in general. It is recommended to add a section in this regard and explain how distribution of body fat may have different impact on inflammation and immune responses. -It is recommended to add a section about metabolically healthy obese (MHO) people and the difference between their inflammation and immune status and obese people with T2DM or metabolic syndrome. - In several places in the text, authors referred to studies on high fat diets or excessive or restricted calorie intake to prove their hypothesis about obesity. Although, an HF diet or excessive calorie intake can be considered as a risk factor for obesity, they are not equal with obesity and several other mechanisms which are beyond the scope of this review (like saturated or unsaturated fats etc.) may cause their alteration of immune responses and not just weight.

Answer:

Thanks for your review and comments. We have submitted the revised manuscript to a professional language editing company for polishing and obtained a new language certificate.

First, as you mentioned in the comments, the distribution of fat in the body is important for the onset and progression of obesity-related type 2 diabetes. We have added the corresponding information to the last paragraph of *"Immune attack in the adipose tissues (AT) of obesity-related T2DM"*. The expansion of subcutaneous adipose tissue in the lower body and adipocyte hyperplasia from precursor cells are a healthy response to high energy storage demands[1-2]. The expansion and inflammatory infiltration of subcutaneous adipose tissue were not associated with obesity-induced insulin resistance according to a recent study[2]. The accumulation of adipose tissue in the upper body, especially in the abdominal cavity, leads to the lipotoxicity and inflammation in insulin-sensitive organs, which mainly contributes to the development of obesity-related metabolic diseases.

Secondly, we readily accepted your comments and suggestions and we have added a new section describing inflammation and immune responses in metabolically healthy obese (MHO)

subjects. MHO may be transitional status and the distribution of adipose tissue seems to be a determinant during the conversion between MHO to metabolic diseases. Compared with the patients with T2DM or other metabolic diseases, MHO subjects usually have more expandability of subcutaneous adipose tissue and less ectopic fat accumulation, which is defined as a healthier phenotype of fat accumulation[3-4]. Besides, lower levels of systematic inflammatory marker, better β-cell secretion capacity and insulin sensitivity could be observed in MHO[3-4]. Many studies also revealed that compared with patients with metabolic diseases, less immune cells infiltration and cytokines production were found in MHO subjects, which was closely associated with less visceral fat mass in the latter[5-6].

As your remind and comments, there were some studies that mention high fat diet/ restricted calorie intake/high fatty acid stimulation, etc., which was not exactly equivalent to obesity. Although high-fat diet is the leading cause of obesity, in many cases, it is difficult to figure out whether it is the diet itself or the occurrence of obesity that causes subsequent pathological changes. We have reviewed the context in relation to this issue in the manuscript. The unclear description was revised for more specific expression, and several irrelevant references and information beyond the scope have been eliminated.

Thanks again for your review and comments!

References

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