

Reviewer 1:

Firstly, thank you for the kindly comments. I have checked the manuscript carefully and revised it according to the comments. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Q1: According to recent studies the title is important and would favor future citations to the paper. What is really new in the paper? What kind of considerations are timely?

Response 1: Thank you for your advice. We have read the review carefully. Previously, we found that the expression of serum haptoglobin changed after treatment of simple obesity patients in clinical trials. However, the specific mechanism of haptoglobin in patients with simple obesity is still unclear. In this review, we introduced recent research progress on haptoglobin, emphasized the relationship between HP and metabolic disease and discussed further research directions of Hp. we have replaced the title. Now it's "Progress on Haptoglobin and Metabolic Diseases".

Q2: Introduction should be less general and focuses in the main message of the review. What are really the recent insights into the paper approach? Moreover, at the end of the intro, it is also not clear what are the major aims of the review paper that should be emphasizing at this stage. After reading the paper several aims are missing. Also in the end of the abstract it should be clear what the new major considerations for this review are. At the introduction a figure or scheme with the chronology or a timeline of the major events in the field, for instance first and/or major studies about Ru in cancer and the last and timely studies?; first studies about haptoglobin and diabetes and/or others diseases and immune responses? This timeline would be interesting and useful for a better understanding of the paper. Moreover, it would also reflect the understanding of the authors about these events. Scheme and/or figures are needed for a better "take home message" of the review. Sometimes, a figure is more than 1000 words.

Response 2: Thank you so much for your advice. We checked the timeline carefully. Haptoglobin was originally discovered in human plasma in 1938. Earlier studies suggested that HP is an acute-phase reactive protein synthesized only in internal organs.

Further studies found that haptoglobin was also expressed in other tissues including endometriosis tissue, white adipose tissue, and colorectal cancer tissues. Previous evidence demonstrated that Hp2 positively correlated with diabetic complications and can be used as a biomarker for simple obesity. Therefore, an increasing number of researchers are committed to exploring the causal relationship between haptoglobin and metabolic diseases to better study the role of haptoglobin and provide new therapeutic methods for the clinical treatment of metabolic syndrome.

Q3: Globally the Discussion section could follow the order of the review. However, is not clear what kind of discussion is referred to this part of the review. It would be better a global conclusion, also with perspectives for future research. Several sentences in the discussion and/or all over the ms are not clear.

Response 3: Thank you for your advice. In this review, we discussed further research directions of Hp. And we have revised several not clear sentences. It's in line 41-50 on page 3, line 78-85 on page 4, line 252-256 on page 10.

Reviewer 2:

Q1: In the manuscript entitled "Considerations on haptoglobin and metabolic diseases", the authors reviewed the recent research progress on haptoglobin with emphasizing the relationship between haptoglobin and the development of metabolic disease. Overall, the review is well-written and the topic is important, but it seemed that this manuscript may be still required some revise 1. Abbreviations (such as "BMI", "LDL", "HDL"..., etc) should be with its full name when it firstly appears in the paper and redundant abbreviations (such as "lipopolysaccharide (LPS)", "monocyte chemotactic protein-1 (MCP-1)"..., etc) should be avoided.

Response 1: Thank you for your advice. We have added full name when abbreviations firstly appears in the paper and deleted the redundant abbreviations.

Q2. Describe Figure legends.

Response 2: Thank you very much for your advice. We added description of figure2 on page 5.

Thank you very much for your valuable comments and looking forward to hearing from

you soon.

Best regards.

Yours sincerely