

**Name of Journal:** *World Journal of Hematology*

**Manuscript NO:** 32446

**Manuscript Type:** Minireviews

**Oxidative alterations in sickle cell disease: Possible involvement in disease pathogenesis**

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#### **Reviewer 1**

Although the review article looks to be structured and worth for publication yet there many references can be deleted with its contents and there are some essential statements all through the review need to be referenced

*We thank to the reviewers for their valuable contributions in the development of our manuscript.*

*We revised the language.*

*We added references .*

*We added some new parts.*

*We showed all the revisions as highlighted.*

#### **Reviewer 2**

This is an interesting review. However, the authors should discuss in more detail about new therapies targeting oxidative alterations in sickle cell disease. In addition, it would be better if the authors can add some figures to demonstrate the major issues they wish to address.

*We added Figure 1.*

#### **Reviewer3**

1) Other factors influence on clinical variability and the pathogenesis of SCD should be addressed in more detail: endothelial dysfunction, related to decreased bioavailability of NO and long periods of ischemia/reperfusion that generate xanthine oxidase from xanthine

dehydrogenase. These conditions led to increased asymmetric dimethylarginine which also, in addition to high oxidation of HbS, influence the formation of free radicals.

*We added these parts to the manuscript and showed as highlighted.*

2) The authors should explain in more detail the role of lipid peroxidation in the disease.

*We added this part to the manuscript file.*

3) When speaking about lipidic products of oxidation, it is necessary to mention something about the relationship between apolipoprotein dysregulation and increased platelet adhesion. For example, the relation between apoA-1 and activation of eNOS (Soupené et al. *Expt Biol Med* 2016; 241:1933-1942).

*We mentioned about the suggested article.*

4) The authors affirm: "There are many oxidative markers being studied in SCD". But almost did not describe them. Also, for a relationship between oxidative markers and clinical variability of the disease, check paper of Rusanova et al. *Eur J Haematol* 2010; 85:529-537. 5)

*We checked that paper.*

The authors should update the references: most of them are from many years ago, and there are no recent ones.

*We added references from recent years.*