March 15th, 2021
World Journal of Diabetes
Editorial Board of Review

The following letter is to present the changes made in the manuscript "**Alzheimer's disease and type 2 diabetes mellitus: pathophysiologic and pharmacotherapeutics links**" according to reviewer suggestions.

We want to thank the reviewers for their corrections and involvement in improving our manuscript. All changes have been marked in red.

Major revisions

1. Authors state that insulin resistance may contribute to the pathogenesis and development of AD and describe key evidence and ongoing trials on the effects of anti-diabetic drugs on cognitive disorders – A long-term condition of insulin resistance may not result in long-lasting diabetes. What are the evidences on the association of insulin resistance (without hyperglycemia) and Alzheimer's disease?
   A: Additional information regarding evidence of the association of AD and insulin resistance without DM has been added to section 4 of the manuscript.

2. The authors list the effects of different anti-diabetic drugs on cognitive status. Effect of diet and exercise should also be included, as they are the first choice of treatment in insulin resistant patients with and without diabetes.
   A: Information regarding the role of exercise and diet on insulin-resistant and diabetic patients has been added to section 5 of the manuscript.

3. Some authors have suggested that the latest antidiabetic drugs, the SGLT2 inhibitors may exert neuroprotective effects by acting on synaptic plasticity. I recommend including SGLT2 inhibitors in the overview of potential beneficial drugs.
   A: Information providing evidence of the role of SGLT2 a neuroprotective agent has been added to section 5 of the manuscript.

4. Regarding antidiabetic drugs, molecules with well-known hypoglycemic effects are mentioned (insulin, sulfonylureas). However, hypoglycemia represents a serious side-effect of these therapies, leading in some cases to major cardiovascular events or death. Moreover, repeated episodes of hypoglycemia are linked to cognitive decline. This aspect should be emphasized as it represents a limitation to the use of these drugs in the treatment of cognitive problems.
   A: Information regarding the hypoglycemic effects of insulin and sulfonylureas as well as the impact of hypoglycemic episodes has been added to section 5 of the manuscript.

Minor Revisions

1. Moreover, numerous complications have been associated with Alzheimer's disease, among which are renal disease, retinopathy, dermopathy, peripheral vasculopathy, and cognitive alterations. These complications have been associated with T2DM, not with Alzheimer's disease.

A: This has been corrected in the introduction of the manuscript.

2. The manuscript is well-written, but it should be revised by a native English speaker, for example: - in 4.1 Other factors, such as the MAPK pathway, GSK-3, insulin-degrading enzyme (IDE), and microvascular dysfunction, also have an important role in tau hyperphosphorylation has to be replaced with: play an important role.
   A: English has been revised and changes have been made accordingly.

Awaiting your positive response,

Juan Salazar, MD.