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Therapeutic repurposing of Pioglitazone for slowing the progression of Mild-Moderate Alzheimer's Disease: A systematic review and meta- analysis

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Pioglitazone is an emerging therapy in treating Alzheimer disease (AD), but there is lack of evidence supporting its efficacy. The objectives of this study were to determine the safety and efficacy of Pioglitazone in slowing the progression of Alzheimer disease in patients with mild-moderate cognitive impairment. This review included Randomized Controlled Trials presenting the comparison between Pioglitazone and a suitable control. An extensive literature search was conducted and eligibility was checked based on the criteria prepared by the researchers. Five studies were included for outcome analysis. The scores of Alzheimer's Disease Assessment Scale- Cognitive subscale (ADAS- Cog) [MD: -2.75; 95% CI: -4.84 to -0.66] showed a statistically significant improvement in cognition. The results of our study prove that Pioglitazone is a potential treatment for AD.

Keywords: Alzheimer's disease; Pioglitazone; Diabetes mellitus; Thiazolidinedione; Oral- hypoglycemic agents

Introduction: Alzheimer's is a neuro- degenerative disease that progresses with age. Though several drug therapies have been identified, they have been ineffective in slowing its progression. The global burden of AD is estimated to be 43.8 million and it has doubled since 1990 [1]. Therapeutic repurposing is an evolving field of research that has identified potential targets for treating AD. It is hypothesized that impaired gluco- regulation can lead to cognitive decline. Various anti- diabetic agents have shown beneficial effects in enhancing regeneration and brain metabolism. Peroxisome Proliferator- Activated Receptor Gamma (PPARγ) agonists can mitigate neuro- degeneration and maintain amyloid beta homeostasis. On comparison with other Thiazolidinediones, Pioglitazone is better tolerated among patients due to its minimal adverse effects and they have better blood brain barrier penetration [2]. This meta- analysis is aimed to evaluate the effectiveness of Pioglitazone for the treatment of AD.

Materials and Methods: An electronic search was conducted in databases such as Cochrane CENTRAL, PubMed and Scopus using keywords like "Thiazolidinediones/therapeutic use" or "Pioglitazone" or "Alzheimers disease/drug therapy" or "cognitive dysfunction/drug therapy. Other sources such as trial registries, cross- referencing and some peer reviewed journals were also searched. Data was extracted using the modified Cochrane data extraction form that was pretested. Trials where Pioglitazone was administered for a minimum duration of six months on older adults with mild to moderate cognitive impairment were eligible for inclusion. The intervention had to be compared to a suitable control like other oral hypoglycemic agents, diabetic diet or placebo for inclusion. The primary outcome was the efficacy of Pioglitazone measured using neuropsychiatric scales. The safety and tolerability of the drug was considered to be the secondary outcome. This was followed by risk of bias assessment (ROB) using Cochrane's ROB assessment tool. The certainty of evidence was evaluated using GradePro; while considering the mean difference, results of bias assessment, consistency and imprecision. The mean and standard deviations of the study data was extracted and computed into Review Manager 5.3 to obtain the mean difference, following which a forest plot was generated. Random effect model was used for outcomes with a high heterogeneity. Sensitivity analysis was also conducted to decrease the level of heterogeneity.

Results and Discussion: A total of 522 articles were screened for eligibility, following which 5 full text articles were included for quantitative analysis. The outcomes Alzheimer's Disease Assessment Scale- Cognitive subscale (ADAS- Cog) and Wechsler Memory Scale- Revised logical memory I (WMS- R) were found to be common in all studies. Pioglitazone did not show a statistically significant improvement in ADAS- Cog scores [Mean Difference (MD): -1.16; 95% Confidence interval (CI): -4.14 to 1.81]. The trials by Sato et al. [3], Hanyu et al. (2009) [4] and Hanyu et al. (2010) [5] showed an improvement in ADAS- Cog scores in patients taking Pioglitazone. However, Hildreth et al. [6] and Geldmacher et al. [7] did not show an improvement in the scores. Sensitivity analysis was conducted with the removal of Hildreth et al., since it had the highest weightage to the pooled analysis, a significant efficacy was obtained (MD: -2.75; 95% CI: -4.84 to -0.66). WMS- R scores had improved significantly in the Pioglitazone group (MD: 2.02; 95% CI: 0.09 to 3.95). Mild- moderate peripheral edema was reported with some patients that did not lead to stoppage of the drug. The other uncommon side effects were upper respiratory tract infection, common cold and hypoglycemia. The ADAS- Cog outcome suggests high evidence in the improvement of cognitive function following treatment with Pioglitazone.

PPARγ agonists have been shown to hinder inflammatory gene expression, alter Aβ homeostasis and display neuro- protective effects [8, 9]. In most of the cases the positive impact of Pioglitazone on cognitive impairment could not be elucidated and exact conclusions not made [10, 11, 12]. Thus, it poses a quality question if it could be effective in tackling the condition of AD.

The current meta-analysis estimated the efficacy of Pioglitazone on patients with AD and cognitive impairment based on the clinical outcomes. Four randomized controlled trials on Pioglitazone in AD were included and the respective outcomes taken into consideration. The efficacy of the same was assessed using ADAS-Cog (MD: 2.75) and WMS-R logical memory (MD: 2.02) scales and a reduced risk of cognitive impairment was found with the use of Pioglitazone. The results of the current analysis can be generalized to wider population since studies that considered co-morbidities as well as concomitant therapies were included. Also, these randomized, controlled trials were conducted throughout the world at multiple centers thereby clearing the ambiguity of the relevance of the results on region specific population.

Foreign language studies as well as unpublished data were excluded from the analysis. Complete research articles of few studies published in unsubscribed journals could not be retrieved and were not included in the review. The studies included had a small sample size, which led to low heterogeneity. These were the few limitations. Instead of symptomatic management, disease-modifying treatment is mandatory in slowing the evolution of AD. The present meta-analysis highlights the fact that Pioglitazone has an improving effect on cognitive function in patients with Alzheimer disease.

Conclusion: Pioglitazone was found to enhance cognition and henceforth slowing the advancement of AD. Besides, the drug was well tolerated with fewer side effects. The results of this study unfold the need for trials to estimate the safety of long term therapy with Pioglitazone in patients with Alzheimer disease. The results of our study suggest that Pioglitazone is a potential therapeutic agent for AD.

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