Regular Article

Apolipoprotein E Gene Polymorphisms Affect the Efficacy of Thiazolidinediones for Alzheimer’s Disease: A Systematic Review and Meta-Analysis

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Although several studies have evaluated the efficacy of thiazolidinediones (TZD) for the treatment of Alzheimer’s disease (AD), investigation of the impact of apolipoprotein E (ApoE) gene polymorphisms on the efficacy of TZD remains insufficient. We investigated the impact by conducting a systematic review and meta-analysis. MEDLINE, Cochrane Library, and Japana Centra Revuo Medicina were searched to identify relevant studies based on eligibility criteria. Mean differences (MD) of Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-Cog) total score with 95% confidence intervals (CI) were calculated for subgroups stratified by ApoE genotype. To evaluate the impact of ApoE gene polymorphisms, meta-regression analysis was also conducted to calculate the regression coefficient (Coef) of ApoE expression status with 95% CI. Three randomized controlled studies comparing rosiglitazone and placebo, with a total of 2381 subjects met the eligibility criteria. ApoE expression status was reported in 983 individuals (ApoE4-positive, 141; ApoE4-negative, 842). When compared to placebo, rosiglitazone significantly decreased ADAS-Cog score in ApoE4-negative individuals (MD, −1.37; 95% CI, −2.09 to −0.65), but significantly increased ADAS-Cog score in ApoE4-positive individuals (MD, 2.18; 95% CI, 0.52 to 3.85). The meta-regression analysis showed a significant association between efficacy and ApoE expression status (Coef, 3.55; 95% CI, 1.42 to 5.68). Although the present results should be interpreted with caution because of the limited number of studies, our findings suggest that ApoE gene polymorphisms impact the efficacy of rosiglitazone for AD patients. This finding would provide useful information for the development of new agents for AD.

Key words Alzheimer’s disease; meta-analysis; meta-regression analysis; rosiglitazone; systematic review; thiazolidinedione

Dementia affects an estimated 47.5 million individuals worldwide, 60–70% of whom have Alzheimer’s disease (AD).1) Currently, although some drugs such as choline esterase inhibitors and memantine are used for treating AD, their efficacy is limited to delaying disease progression or relieving symptoms.2) One reason for these limitations may be the fact that AD pathogenesis remains unclear. Therefore, despite the lack of established treatment, drug development has faced difficulties.3) Several recent studies have reported an association between AD and diabetes mellitus (DM).4–6) These studies demonstrated insulin resistance in the central nervous system (CNS) in some AD patients, which contributed to impaired cognitive functions. This association has been termed type 3 diabetes (DM).4–6) Among these agents, thiazolidinediones (TZD) exhibited various favorable effects in in vitro and in vivo studies.7–10) These agents contributed to clearing of amyloid beta protein through apolipoprotein E (ApoE) function.11) Some reports of clinical trials indicated that TZD improved cognitive function in AD patients.12–14) Additionally, a systematic review and meta-analysis concluded that the efficacy of TZD was significant.15) Although the efficacy of TZD has been demonstrated, the clinical relevance is limited because the efficacy is lower than that of choline esterase inhibitors.

ApoE is a lipoprotein that has genetic polymorphisms (ApoE2, ApoE3, and ApoE4).16–18) The wild-type ApoE3 constitutes 50–90% of individuals, whereas ApoE4 that constitutes 5–35% of individuals is known to be a genetic risk factor of AD.19) A clinical trial using intranasal insulin for AD showed improved cognitive function in ApoE4-negative AD patients following short-term intranasal insulin treatment,20) suggesting that the therapeutic efficacy may be affected by ApoE gene polymorphisms. Moreover, this study discussed that ApoE4-negative AD patients may be more sensitive to insulin in the CNS than ApoE4-positive patients. This finding suggests that ApoE gene polymorphisms may contribute to inter-individual variability in AD pathogenesis, and implies a relation of ApoE gene polymorphisms to insulin sensitivity in the CNS. If the type 3 DM hypothesis depends on ApoE gene polymorphisms, the efficacy of TZD on the treatment of AD would also be affected by ApoE gene polymorphisms. An investigation into this possibility could lead to identification of the appropriate population for treatment and elucidation of AD pathogenesis, even though the efficacy of TZD for AD is limited. However, subgroup analyses stratified by ApoE genotype in clinical trials of TZD have not fully determined whether ApoE gene polymorphisms affect therapeutic response because the results of previous reports were contradictory and inconclusive.21–23) Therefore, we conducted a systematic re-

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view and meta-analysis on previous clinical studies to examine whether ApoE gene polymorphisms affect the efficacy of TZD for AD.

METHODS

Search Strategy and Eligible Criteria  Two reviewers (RI and KO) independently searched MEDLINE, Cochrane Library, and Japana Centra Revuo Medicina (Ichi-shi Web) to identify relevant studies using the following terms: (thiazolidinediones or rosiglitazone or pioglitazone) AND (dementia or cognitive impairment or Alzheimer’s disease) AND apolipoprotein E. The search period was from 1966 to October 2017. The literature search was complemented by searching the following clinical trial registries: ClinicalTrials.gov, ALOIS, and Japanese National University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR). Manual search was also conducted on the references in identified articles.

We planned to include randomized controlled trials (RCT) that met following criteria: (1) RCT investigating the efficacy of TZD for AD; (2) RCT using Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-Cog) as endpoint measure; (3) RCT examining and reporting ApoE gene polymorphisms of participants. Language restriction was not applied.

When the search results differed between the two reviewers, they discussed until achieving agreement. In the case of not achieving agreement, another reviewer (KS) made the final decision.

Data Extraction  Two reviewers (RI and KO) independently extracted the following data: first author, publication date, study design, study duration, inclusion criteria, exclusion criteria, number of participants, ApoE4 expression status (positive or negative), age, gender, disease severity, comorbidities, dosing information of TZD, concomitant medications, and ADAS-Cog total score before and after the intervention.

Quality Assessment  The quality of each included study was independently evaluated by two reviewers (RI and KO) based on the Jadad score24,25) and the Cochrane Collaboration’s tool for assessing risk of bias.26) The Jadad scores range from 0 to 5, obtained by scoring items regarding randomization (scores 0 to 2), blinding (scores 0 to 2), and an account of all participants (scores 0 to 1). A score of 3 or higher generally indicates good quality.

Statistical Analysis  Relevant study characteristics were summarized using descriptive statistics. Continuous variables are expressed as mean, and categorical variables as frequency and percentage (%).

The endpoint was the change in ADAS-Cog total score from baseline (minus value indicates cognitive function improvement). To appropriately calculate the pooled estimates of mean differences (MD) and 95% confidence intervals (CI), the method of data synthesis was determined based on $I^2$ statistics that indicates the heterogeneity among included studies calculated from all available participant data. If $I^2$ statistics was lower than 50%, the data were synthesized using the inverse variance method to calculate the pooled estimates. If $I^2$ statistics was equal or higher than 50%, the data were synthesized using the DerSimonian–Laird method to calculate the pooled estimates. After determining the data synthesis method, pooled estimates and $p$ value were calculated in each group stratified by ApoE genotype.

A meta-regression analysis was also conducted to investigate the influence of ApoE gene polymorphisms. The regression coefficient (Coef), 95% CI, and $p$ value were calculated using ApoE4 expression status (positive vs. negative) as the independent variable and the change in ADAS-Cog total score from baseline as the dependent variable.

Publication bias was examined by contour-enhanced funnel plots combined with the trim and fill method.27) The contour-enhanced funnel plot is a method that takes into account the significant level of the result from each included study. The resulting funnel plot showing an asymmetric distribution (an asymmetric funnel) indicates potential publication bias or other biases or factors affecting the study results according to the areas generating the asymmetry. The trim and fill method visually complements missing studies detected statistically in the funnel plot. If the complementary plots appear in areas of statistical non-significance, this implies a possibility that the asymmetry is caused by factors other than publication bias. Conversely, if the plots appear in areas of statistical significance, this implies that the asymmetry is caused by publication bias. If no complementary plots appear in the funnel plot, this implies that asymmetry in the funnel plot is not detected statistically.

A $p$ value less than 0.05 was considered statistically significant. All statistical analyses were conducted using STAT A/SE 13.0 software (StataCorp LP, College Station, TX, U.S.A.).

RESULTS

Identification and Characteristics of Included Studies  Nine studies were identified as potential candidates for this study (Fig. 1). Five studies remained after removing duplicates. Among them, one study was excluded upon screening the title and abstract because the report was an abstract of a conference, and one study was excluded upon reading the full text because it was a post-hoc analysis of another eligible study.
Eventually, three studies with a total of 2381 participants were included in the analysis. The major characteristics of the included studies are shown in Table 1. Of all participants, 1974 were analyzed for efficacy. Moreover, ApoE4 expression status was reported in 983 subjects (ApoE4-positive, 141; ApoE4-negative, 842). All included studies compared the efficacy of rosiglitazone against placebo for mild to moderate AD. The duration of administration ranged from 24 to 48 weeks. In all three studies, two or three dosages of rosiglitazone were compared with a placebo group, and the results were reported for each dosage.

Quality Assessments

Quality evaluations are summarized in Table 1 that shows the Jadad score, and in Fig. 2 that presents the results of the Cochrane Collaboration’s tool for assessing risk of bias. The Jadad scores of the included studies ranged from 3 to 4. Two studies used the permuted block randomization method, whereas one study did not report the allocation method. Although all three studies adopted double-blind procedures, the manner by which blinding was maintained was unclear. Statistical analyses were conducted based on the intention-to-treat principle in all three studies.

Meta-Analyses and Meta-Regression Analysis

A meta-analysis for heterogeneity using all available participant data indicated no evidence of heterogeneity ($I^2$ statistics, 0%) (Fig. 3). The result based on three different dosage groups from three studies also showed that rosiglitazone significantly decreased ADAS-Cog score (MD, $-0.53; 95\%$ CI, $-1.01$ to $-0.06$; $p=0.03$). Regarding the meta-analysis stratified by ApoE4 expression status, rosiglitazone significantly decreased ADAS-Cog score in ApoE4-negative subjects, based on three different dosage groups from three studies (MD, $-1.37; 95\%$ CI, $-2.09$ to $-0.65$; $p<0.001$) (Fig. 4). Moreover, when meta-analysis was conducted after stratifying ApoE4-negative subjects by rosiglitazone dosage into 2 and 8 mg groups reported in the three studies, the estimates obtained from the two dosage groups (2 mg group: MD, $-1.61; 95\%$ CI, $-2.64$ to $-0.59$; $p=0.002$. 8 mg group: MD, $-0.92; 95\%$ CI, $-2.02$ to $0.19$; $p=0.10$, respectively) (Supplementary material) were consistent with the estimate obtained from ApoE4-negative subjects for all dosages. On the other hand, rosiglitazone significantly increased ADAS-Cog score in ApoE4-positive subjects, based on three different dosage groups from one study (MD, $2.18; 95\%$ CI, $0.52$ to $3.85$; $p<0.001$) (Fig. 5). For ApoE4-positive subjects, meta-analysis after stratification by rosiglitazone dosage was not possible because data were only available from a single report.

A meta-regression analysis showed a significant association between the change in ADAS-Cog score and ApoE4 expression status (Coef, $3.55; 95\%$ CI, $1.42$ to $5.68$, $p=0.005$).

Publication Bias

The contour-enhanced funnel plot using all available participant data showed an asymmetric plot implying a possibility that studies that had a negative impact of rosiglitazone on ADAS-Cog score were not included in the present study for some reason (Fig. 6). However, when we used the trim and fill method to identify missing studies statistically, no studies needed to be filled in the funnel plot, indicating that there were no missing studies that would have
DISCUSSION

We conducted a systematic review and meta-analysis to clarify whether ApoE gene polymorphisms affect the efficacy of TZD for AD. Similar to the results of a previous meta-analysis, the present study shows that rosiglitazone significantly decreases ADAS-Cog score compared to placebo. 18 All three studies included in analysis were evaluated to be high-quality reports. Additionally, heterogeneity was not observed in this result based on $I^2$ statistics. The three studies consistently accounted for publication bias or other biases.

Fig. 3. Forest Plot of the Changes in Alzheimer’s Disease Assessment Scale-Cognitive Subscale Scores in all Subjects Who Received Rosiglitazone Compared with Placebo

CI, confidence interval; IV, inverse variance; WMD, weighted mean difference.

Fig. 4. Forest Plot of the Changes in Alzheimer’s Disease Assessment Scale-Cognitive Subscale Scores in ApoE4-Negative Subjects Who Received Rosiglitazone Compared with Placebo

CI, confidence interval; IV, inverse variance; WMD, weighted mean difference.
support the hypothesis that rosiglitazone improves cognitive function in mild to moderate AD patients.

However, when stratifying participants by ApoE4 expression status, pooled point estimates of MDs indicated opposite effects of rosiglitazone in ApoE4-positive and -negative subjects. Rosiglitazone treatment decreased ADAS-Cog score in ApoE4-negative subjects compared to placebo, but increased ADAS-Cog score in ApoE4-positive subjects. The meta-regression analysis also suggests that ApoE4 expression status affects the change in ADAS-Cog score. These results indicate that while rosiglitazone truly improves cognitive function in ApoE4-negative AD patients, it impairs or does not change cognitive function in ApoE4-positive patients. A previous animal study demonstrated a similar tendency. When pioglitazone was administered to ApoE transgenic mice, the change in tau phosphorylation differed between ApoE3 transgenic
mice and ApoE4 transgenic mice; tau phosphorylation was significantly reduced in ApoE3 transgenic mice, but increased in ApoE4 transgenic mice. The results of the present and previous studies may indicate that the efficacy of TZD for AD depends on ApoE gene polymorphisms.

Furthermore, although the point estimate of MD obtained from ApoE4-negative subjects was still clinically limited when compared with choline esterase inhibitors, clinical trial has not clearly demonstrated a significant effect of ApoE genotype on treatment response to choline esterase inhibitors. The difference in effect of ApoE gene polymorphism on cognitive response between TZD and choline esterase inhibitors may provide useful information to facilitate drug development for AD. A study reported that some AD patients have low proportion of ApoE4 expression and their cognitive impairment may be related to DM or its pathogenesis. Thus, clinical trials of TZD or other antidiabetic agents for the treatment of AD probably should target the ApoE4-negative population because these drugs would be more effective in this population. Additionally, this finding may lead to elucidation of AD pathogenesis or a new definition of dementia.

However, the present study had several limitations. A major limitation was that the number of studies analyzed was relatively small even though each study included at least 100 participants. The meta-analysis for ApoE4-positive subjects was conducted using data obtained from a portion of participants in only one study. Although the trim and fill method yielded no plots indicating the existence of unpublished studies showing a negative impact of rosiglitazone on cognitive function, reliance on the results of one study could lead to biased results. Thus, the influence of rosiglitazone on cognitive function in ApoE4-positive AD patients remains unclear. The result of the meta-regression analysis was also inconclusive for the same reason.

Another limitation was that the existence of publication bias was not fully excluded. We attempted to conduct a systematic search, and no evidence of publication bias was detected statistically on the contour-enhanced funnel plot combined with the trim and fill method. However, the funnel plot requires at least 10 studies for accurate detection of a publication bias. It is possible that we missed some relevant studies in our literature search. Additional studies would solve this limitation by complementing the funnel plot.

Additionally, for a given study, we calculated the pooled estimates for various dosages of rosiglitazone using the same data of the placebo arm repeatedly in the meta-analysis and meta-regression analysis. This may lead to overestimation of the precision of pooled MDs. Therefore, the observed statistical significance should be interpreted carefully. Although the same applies to the analysis of ApoE4-negative subjects, the result seems to be more reliable because the three studies showed consistent results without any heterogeneity. Moreover, a subgroup analysis in ApoE4-negative subjects stratified by rosiglitazone dosage showed statistically significant decreases in ADAS-Cog at 2 mg of rosiglitazone, and the same tendency at 8 mg. Additional studies targeting ApoE4-negative AD patients are needed to confirm the hypothesis proposed in the present study.

Our findings suggest that ApoE gene polymorphisms affect the efficacy of rosiglitazone, a representative TZD, for the treatment of mild to moderate AD. Particularly, rosiglitazone may be effective in ApoE4-negative AD patients. Future studies targeting ApoE4-negative AD patients should be conducted to confirm the present findings. The present results may provide important information for the development of new therapies and elucidation of AD pathogenesis.

**Conflict of Interest** The authors declare no conflict of interest.

**Supplementary Materials** The online version of this article contains supplementary materials.

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