REVIEW

Safety and efficacy of intranasal insulin in patients with Alzheimer’s disease: a systematic review and meta-analysis

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Abstract

**Background and aim:** We performed this meta-analysis to evaluate the safety and efficacy of intranasal insulin in Alzheimer's disease (AD) patients.

**Methods:** A literature search was conducted for PubMed, Scopus, and Web of Science from inception till August 2022. Documents were screened for qualified articles, and all concerned outcomes were pooled as risk ratios (RR) or mean difference (MD) in the meta-analysis models using Review Manager (RevMan version 5.4).

**Results:** Our results from 12 studies favored intranasal insulin over placebo in terms of Alzheimer Disease’s Assessment Scale-cognitive subscale (ADAS-cog) 20IU, (MD = -0.13, 95% CI [-0.22, -0.05], P = 0.003). The overall effect did not favor either of the two groups for ADAS-cog 40IU, memory composite 20IU and 40IU, and adverse events. (MD = -0.08, 95% CI [-0.16, 0.01], P = 0.08), (MD = 0.65, 95% CI [-0.08, 1.39], P = 0.08), (MD = 0.25, 95% CI [-0.09, 0.6], P = 0.15), (MD = 1.28, 95% CI [0.75, 2.21], P = 0.36), respectively.

**Conclusion:** Ultimately, this meta-analysis showed that intranasal insulin in small doses (20IU) significantly affects patients with AD. Further studies are recommended on reliable insulin delivery devices to increase insulin in the central nervous system.

**Relevance for patients:** Intranasal insulin has shown promising results in treating patients with AD. The lower doses (20 IU) can play a positive role in improving the disease. As research continues, it is likely that this treatment will become more widely accepted and utilized in clinical practice.

**Keywords:** Alzheimer's disease, Intranasal insulin, Mild cognitive impairment
1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative illness characterized by changes in behavior and personality, cognitive impairment, and memory loss [1]. Major neuropathological features of AD are thought to be the buildup of extracellular amyloid/senile plaques made of intracellular neurofibrillary tangles and amyloid-(A). It is worth mentioning that AD-sensitive brain areas exhibit substantial abnormalities in glucose metabolism and reduced neuron use of glucose as a result of disruptions in the insulin signaling pathway [2].

Several studies recently suggested that insulin may be essential in preserving the brain's mitochondrial balance and cerebral bioenergetics [3]. In addition, it could have an impact on the clearance of the significant factors in the path mechanism of AD, including amyloid peptide and tau protein phosphorylation [3]. Low insulin levels in the CNS may be caused by impaired insulin transport through the blood-brain barrier (BBB). Therefore, raising brain insulin may stop the degenerative processes associated with AD [3]. Based on that, a wide range of pharmacological substances and delivery strategies have been developed and studied.

The olfactory bulb, cerebral cortex, hippocampus, hypothalamus, cerebellum, and choroid plexus have the highest insulin receptor density [4]. Accordingly, through the roof of the nose, insulin can cross through the BBB and systemic circulation, entering the brain via the olfactory, trigeminal, and nerve fiber pathways [5].

Binding insulin with its receptor will lead to autophosphorylation of the insulin receptor and induction of insulin receptor substrate (IRS). Activation of AKT, which is one of the signaling routes that insulin activates, through IRS phosphorylation has been linked to improvements in neuronal protection, learning, and memory functions among AD patients [6].
However, several previous studies have shown conflicting findings regarding the influence of intranasal insulin on dementia in AD patients. Therefore, in this study, we aimed to fill the gap in detecting the real effect of intranasal insulin on these patients.

2. Materials and methods

This systematic review and meta-analysis were reported following the PRISMA declaration requirements [7]. The protocol of this study was registered on the PROSPERO (CRD42022355827).

2.1. Eligibility criteria

The following conditions were considered for the study:

Population: studies on patients who have AD or mild cognitive impairment

Intervention: studies where the exposed group was intranasal insulin.

Comparator: studies where the control group received a placebo.

Outcome: studies stated one or more of the following outcomes: Alzheimer Disease’s Assessment Scale–cognitive subscale (ADAS-cog) either 40IU or 20 IU, and adverse effects (headache, fall, and rhinitis/upper respiratory infection (URI)). Additionally, Memory composite (delayed story recall) 40IU and 20IU, Dementia Severity Rating Scale (DSRS), Alzheimer’s Disease Cooperative Study–activities of daily living (ADCS-ADL), Clinical Dimension Rating–Sum of Boxes (CDR-SOB), and Cerebral Spinal Fluid (CSF) Biomarkers of AD.

Study design: studies that were designated as randomized clinical trials (RCTs).

Studies excluded: not published in the English language, comments, review articles, case reports, observational studies, abstracts, and letters to the editor.

2.2. Search strategy
Three electronic databases (PubMed, Scopus, and Web of Science) were searched from their inception until August 2022 using the following query: (Alzheimer OR (Senile Dementia) OR (Dementia Presenile)) AND (Insulin OR Novolin OR Iletin)

2.3. Selection process

The titles and abstracts of all citations considered for inclusion were reviewed by three authors independently. Then, we extracted the full text of the selected studies to evaluate their applicability and validated them according to our systematic review and meta-analysis standards. Discrepancies were resolved by consensus.

2.4. Data extraction

Data were extracted from an online data extraction sheet by four independent authors. The extracted data included: (1) a summary of the included studies, (2) baseline characteristics for the included population, (3) risk of bias domains, and (4) outcome measures. Any disagreements were solved by a fifth author.

2.5. Quality appraisal

We used the Cochrane assessment tool 2 (ROB2) for randomized controlled trials [8]. Using that tool, each study was assessed for the possibility of bias in the following domains: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants, personnel, and outcome assessors, 4) incomplete outcome data, 5) selective outcome data reporting, and 6) other sources of bias. The degree of bias in the authors' conclusions is classified as "low risk," "some concerns," or "high risk".

2.6. Synthesis methods

Continuous were pooled as mean difference (MD) between the two groups from baseline to the endpoint in the meta-analysis models utilizing the inverse variance (IV) method. We assumed a fixed-effect model of the MD as the main analysis model. Nevertheless, relative risk (RR) was used to pool dichotomous data in a fixed-effect model using the Mantel-Haenszel (M-H) method. RevMan software (version 5.4 for
Windows) was applied to run the statistical analysis. In addition, we used the Chi-square test (Cochrane Q test) to assess the statistical heterogeneity of the included studies. Significant heterogeneity was reflected by I-square > 50% with a P value less than 0.1.

3. Results

3.1. Results of study selection and characteristics

Our literature search process retrieved 9119 records. After removing duplicates, 6391 abstracts were evaluated, and 19 articles were eligible for full-text screening. Of them, 12 studies were included in this study. Due to the heterogeneity in some included studies, we conducted a meta-analysis of seven studies. The PRISMA flow diagram of the study selection process is shown in Figure 1.

The number of patients who were included in the meta-analysis was 620, including 382 who were treated with intranasal insulin and 238 who received a placebo. A summary of the eligible studies and the characteristics of their patients are presented in Table 1 and Table 2.

3.2. Quality assessment

According to RoB2, we found four studies with an overall low risk of bias [9–12], and eight had some concerns. The reasons for some concerns are that four studies had some concerns in the randomization process [13–16] and four had some concerns in the selection of the reported results [17–20] Figure 2.

3.3. Outcomes

3.3.1. ADAS-cog 40IU

Six studies were reported for ADAS-cog 40IU with a total of 486 participants. The findings presented that there was no significant difference between the intranasal insulin and the placebo according to
ADAS-cog 40IU. The MD was -0.08 (95% CI -0.16 to 0.01, P = 0.08). The pooled studies were homogenous (I² = 0%, P = 0.92), Figure 3A.

3.3.2. ADAS-cog 20IU

Three studies represented ADAS-cog 20IU with a total of 191 participants. Pooled studies favored the insulin effect over the placebo. The MD was -0.13 (95% CI -0.22 to -0.05, P = 0.003). The results were homogenous (I² = 0%, P = 0.86), Figure 3B.
Figure 1. PRISMA flow diagram of studies’ screening and selection
Figure 2. The risk of bias summary and risk of bias graph according to the Cochrane Risk of Bias assessment tool.
Table 1. Summary of the included studies.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Design</th>
<th>Country</th>
<th>Duration (months)</th>
<th>Patient’s eligibility</th>
<th>Type of insulin</th>
<th>Outcomes measured</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claxton 2015[15]</td>
<td>RCT</td>
<td>United States</td>
<td>24</td>
<td>Patients with mild cognitive impairment or Alzheimer's disease.</td>
<td>Levemir; Novo Nordisk, Princeton, New Jersey</td>
<td>Primary: A verbal memory composite score; Secondary: executive function; visuospatial working memory; caregiver-rated functional ability; Metabolic outcomes</td>
<td>Intranasal insulin improves AD.</td>
</tr>
<tr>
<td>Craft 2012[11]</td>
<td>RCT</td>
<td>United States</td>
<td>6</td>
<td>Patients who scored between 0.5 and 1 on the Clinical Dementia Rating; Who &gt;15 on the Mini-Mental State Examination.</td>
<td>Novolin R; Novo Nordisk, Princeton, New Jersey</td>
<td>Primary: delayed story recall; DSRS; Metabolic outcomes</td>
<td>Intranasal insulin improves MCI and AD.</td>
</tr>
<tr>
<td>Craft 2017[14]</td>
<td>RCT</td>
<td>United States</td>
<td>4</td>
<td>Patients who were probably AD; Who &gt;15 on the Mini-Mental State Examination.</td>
<td>Humulin R U-100, Eli Lilly and Co.; Levemir®; Novo Nordisk, Princeton, New Jersey</td>
<td>Primary: delayed story recall; Secondary: ADAS-Cog; DSRS; MRI volume changes in AD-related regions of interest</td>
<td>Intranasal insulin improves AD.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Location</td>
<td>Sample Size</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Primary Outcomes</td>
<td>Secondary Outcomes</td>
</tr>
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</tr>
<tr>
<td>Craft 2020[10]</td>
<td>RCT</td>
<td>United States</td>
<td>48</td>
<td>Adults between the ages of 55 and 85, Patients with mild cognitive impairment or Alzheimer's disease, MMSE scores of 20 or higher, Global clinical dementia ratings of 0.5 or 1.0</td>
<td>Logical memory-delayed scores falling within a predetermined education-adjusted range.</td>
<td>Humulin RU-100; Lilly</td>
<td>ADAS-Cog</td>
</tr>
<tr>
<td>Rosenbloom 2014[16]</td>
<td>Randomized, cross-over</td>
<td>United States</td>
<td>6</td>
<td>Mild-moderate Alzheimer's disease (AD), Who are &gt;65 years old and 85 years old, The Clinical Dementia Rating (CDR) for each individual ranged from 1 to 2</td>
<td></td>
<td>Rapid Acting Insulin</td>
<td>ADAS-Cog, CDR-SB</td>
</tr>
<tr>
<td>Rosenbloom 2021[12]</td>
<td>RCT</td>
<td>United States</td>
<td>6</td>
<td>Patients with mild cognitive impairment or Alzheimer's disease, Montreal Cognitive Assessment (MoCA) scores of 18–27.</td>
<td></td>
<td></td>
<td>ADAS-Cog, CDR-SB</td>
</tr>
<tr>
<td>Mustapic 201[13]</td>
<td>RCT</td>
<td>United States</td>
<td>4</td>
<td>Patients aged 55 or greater, Patients with mild cognitive impairment or Alzheimer's disease, Who is on stable doses of Memantine (Namenda) or cholinesterase inhibit</td>
<td></td>
<td></td>
<td>ADAS-Cog, Mini-Mental State Examination, Alzheimer's disease Assessment Scale for cognition and insulin signalling mediators as biomarkers, especially EV biomarkers of insulin resistance as (pS312-IRS-1 and pY-IRS-1).</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Country</td>
<td>Subjects</td>
<td>Inclusion Criteria</td>
<td>Outcomes</td>
<td></td>
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<tr>
<td>Kellar 2022[20]</td>
<td>RCT</td>
<td>United States</td>
<td>Adults between the ages of 55 and 85, Patients with mild cognitive impairment or Alzheimer's disease, MMSE scores of 20 or higher, Global clinical dementia ratings of 0.5 or 1.0, Logical memory-delayed scores falling within a predetermined education-adjusted range.</td>
<td>CSF macrophage-derived chemokine, CSF interferon-γ, CSF immune/inflammatory/vascular markers, changes in cognition, brain volume, and amyloid and tau concentrations, CSF markers of inflammation, immune function, and vascular integrity, assessed their relationship with changes in cognition, brain volume, and CSF amyloid and tau concentrations, reduced interleukin-6, cerebral spinal fluid (CSF) biomarker profile, and slower symptom progression.</td>
<td>Intranasal insulin improves MCI and AD.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reger 2008[18]</td>
<td>RCT</td>
<td>United States</td>
<td>NR</td>
<td>Patients with mild cognitive impairment or Alzheimer's disease</td>
<td>Verbal memory, Verbal Memory, Plasma β-Amyloid, Plasma insulin and glucose levels.</td>
<td>Intranasal insulin improves MCI and AD.</td>
<td></td>
</tr>
<tr>
<td>Reger 2007[17]</td>
<td>RCT</td>
<td>United States</td>
<td>NR</td>
<td>Patients with mild cognitive impairment or Alzheimer's disease</td>
<td>Primary: intended to be verbal memory after a delay, Attention, caregiver assessments of functional state. Secondary: plasma levels of insulin, glucose, beta-amyloid, and cortisol.</td>
<td>Intranasal insulin improves MCI and AD.</td>
<td></td>
</tr>
<tr>
<td>Reger 2006[19]</td>
<td>RCT</td>
<td>United States</td>
<td>NR</td>
<td>There were no neurological disorders (other than AD)</td>
<td>Primary: Novolin R containing cresol, Novo Nordisk.</td>
<td>Intranasal insulin improves AD.</td>
<td></td>
</tr>
</tbody>
</table>
### Abbreviation:

Apo e4, Apolipoprotein E4; DSRS, Dementia Severity Rating Scale; ADAS-cog, Alzheimer Disease’s Assessment Scale–cognitive subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study–activities of daily living; CDR-SOB Clinical Dimension Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; NR, not reported; AD, Alzheimer’s disease; MCI, mild cognitive impairment; CSF, cerebral spinal fluid; COWAT, Controlled Oral Word Association Test; WMS-IV, Wechsler Memory Scale.
Table 2. Baseline characteristics for the population of the included studies.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Groups</th>
<th>No of participants</th>
<th>Age Mean (SD)</th>
<th>sex(m/f)</th>
<th>BMI Mean (SD)</th>
<th>Education Mean (SD)</th>
<th>Apo e status N (%)</th>
<th>Diagnosis MCI/AD Mean (SD)</th>
<th>DSRS Mean (SD)</th>
<th>ADAS-cog Mean (SD)</th>
<th>ADCS-AD Mean (SD)</th>
<th>Delayed story recall score Mean (SD)</th>
<th>MMSE Mean (SD)</th>
<th>CDR-SOB Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craft 2012[11]</td>
<td>Placebo</td>
<td>30</td>
<td>74.9 (8.7)</td>
<td>17/13</td>
<td>27.4 (4.3)</td>
<td>15.3 (3.2)</td>
<td>13 (44.8)</td>
<td>21/9</td>
<td>1.64 (1.04)</td>
<td>1.93 (0.76)</td>
<td>3.75 (0.16)</td>
<td>2.25 (1.04)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Craft 2012[11]</td>
<td>20 IU of Insulin</td>
<td>36</td>
<td>72.8 (9)</td>
<td>22/14</td>
<td>26.7 (4.8)</td>
<td>15.5 (3.0)</td>
<td>18 (50)</td>
<td>20/16</td>
<td>1.72 (0.96)</td>
<td>2.21 (0.72)</td>
<td>3.79 (0.18)</td>
<td>1.86 (1.02)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Craft 2012[11]</td>
<td>40 IU of Insulin</td>
<td>38</td>
<td>69.9 (8.6)</td>
<td>20/18</td>
<td>26.9 (4.3)</td>
<td>16.2 (3.03)</td>
<td>16 (42.1)</td>
<td>23/15</td>
<td>1.78 (1.04)</td>
<td>2.26 (0.73)</td>
<td>3.77 (0.18)</td>
<td>1.99 (1.04)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Craft 2017[14]</td>
<td>Placebo</td>
<td>12</td>
<td>68.4 (8.9)</td>
<td>6/6</td>
<td>26.7 (3.3)</td>
<td>16.5 (2.0)</td>
<td>8 (66.66)</td>
<td>8/4</td>
<td>7.3 (6.9)</td>
<td>20 (11.7)</td>
<td>NR</td>
<td>NR</td>
<td>24.8 (4.2)</td>
<td>NR</td>
</tr>
<tr>
<td>Craft 2017[14]</td>
<td>Regular insulin</td>
<td>12</td>
<td>70.5 (9.1)</td>
<td>7/5</td>
<td>28.8 (6.1)</td>
<td>15.6 (2.8)</td>
<td>8 (66.66)</td>
<td>7/5</td>
<td>7.7 (6.8)</td>
<td>19.8 (12.8)</td>
<td>NR</td>
<td>NR</td>
<td>26 (3.7)</td>
<td>NR</td>
</tr>
<tr>
<td>Craft 2017[14]</td>
<td>detemir</td>
<td>12</td>
<td>67.3 (7.8)</td>
<td>6/6</td>
<td>29.4 (6.6)</td>
<td>14.8 (2.4)</td>
<td>6 (50)</td>
<td>7/5</td>
<td>8.7 (6.7)</td>
<td>21.6 (13.7)</td>
<td>NR</td>
<td>NR</td>
<td>25.2 (4.1)</td>
<td>NR</td>
</tr>
<tr>
<td>Craft 2020[10]</td>
<td>Placebo (blind)</td>
<td>119</td>
<td>71.1 (6.8)</td>
<td>61/58</td>
<td>NR</td>
<td>16.3 (2.9)</td>
<td>77 (64.7)</td>
<td>46/73</td>
<td>NR</td>
<td>24.73 (7.56)</td>
<td>NR</td>
<td>NR</td>
<td>24.84 (2.72)</td>
<td>3.35 (1.51)</td>
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<tr>
<td>Craft 2020[10]</td>
<td>Placebo (open-label)</td>
<td>104</td>
<td>71 (7.0)</td>
<td>53/51</td>
<td>NR</td>
<td>16.4 (2.8)</td>
<td>65 (62.5)</td>
<td>41/63</td>
<td>NR</td>
<td>24.07 (7.3)</td>
<td>NR</td>
<td>NR</td>
<td>24.93 (2.73)</td>
<td>3.31 (1.53)</td>
</tr>
<tr>
<td>Craft 2020[10]</td>
<td>Insulin (blind)</td>
<td>121</td>
<td>70.5 (7.4)</td>
<td>62/59</td>
<td>NR</td>
<td>16.1 (2.6)</td>
<td>79 (65.3)</td>
<td>41/80</td>
<td>NR</td>
<td>25.91 (8.28)</td>
<td>NR</td>
<td>NR</td>
<td>24.79 (2.75)</td>
<td>3.59 (1.51)</td>
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<tr>
<td>Craft 2020[10]</td>
<td>Insulin (open-label)</td>
<td>106</td>
<td>70.3 (7.3)</td>
<td>57/49</td>
<td>NR</td>
<td>16.1 (2.7)</td>
<td>72 (67.9)</td>
<td>35/71</td>
<td>NR</td>
<td>25.34 (8.25)</td>
<td>NR</td>
<td>NR</td>
<td>24.95 (2.7)</td>
<td>3.56 (1.45)</td>
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<tr>
<td>Author</td>
<td>Year</td>
<td>Treatment</td>
<td>Dose</td>
<td>Placebo</td>
<td>Normal E4−</td>
<td>Normal E4+</td>
<td>Memory-impaired E4−</td>
<td>Insulin</td>
<td>Memory-impaired E4+</td>
<td></td>
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<tr>
<td>Claxton</td>
<td>2013</td>
<td>Placebo</td>
<td>30</td>
<td>14.84 (10.09)</td>
<td>13/13</td>
<td>27.39 (4.3)</td>
<td>15.26 (3.23)</td>
<td>13 (43.3)</td>
<td>61/40</td>
<td>7.17 (5.59)</td>
<td>2.05 (0.97)</td>
<td>43.7 (6.8)</td>
<td>11.27 (7.6)</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td>20 IU of Insulin</td>
<td>36</td>
<td>72.8 (7.5)</td>
<td>22/14</td>
<td>26.7 (4.1)</td>
<td>15.5 (3.5)</td>
<td>18 (50)</td>
<td>64/40</td>
<td>7.16 (4.28)</td>
<td>2.21 (0.63)</td>
<td>44.17 (5.38)</td>
<td>9.3 (8.36)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 IU of Insulin</td>
<td>18</td>
<td>69.8 (9.12)</td>
<td>20/18</td>
<td>26.8 (4.9)</td>
<td>16.2 (2.8)</td>
<td>16 (42.1)</td>
<td>64/40</td>
<td>7.57 (5.36)</td>
<td>2.22 (0.65)</td>
<td>43.5 (6.61)</td>
<td>10.55 (8.23)</td>
<td>NR</td>
</tr>
<tr>
<td>Claxton</td>
<td>2015</td>
<td>Placebo</td>
<td>20</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
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<td>20 IU of Insulin</td>
<td>21</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
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<tr>
<td></td>
<td></td>
<td>40 IU of Insulin</td>
<td>19</td>
<td>NR</td>
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<td>Rosenbloom</td>
<td>2014</td>
<td>Insulin</td>
<td>19</td>
<td>68.4 (8.1)</td>
<td>10</td>
<td>9</td>
<td>25 (4.4)</td>
<td>NR</td>
<td>NR</td>
<td>14/21</td>
<td>NR</td>
<td>23.2 (5.4)</td>
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<tr>
<td>Rosenbloom</td>
<td>2021</td>
<td>Saline</td>
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<td>74.4 (6.4)</td>
<td>10</td>
<td>6</td>
<td>24.5 (3.6)</td>
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<td>NR</td>
<td>9/10</td>
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<td>Mustapic</td>
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<td>26</td>
<td>76.2 (9.06)</td>
<td>11</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
<td>23 (50)</td>
<td>69/31</td>
<td>NR</td>
<td>1.93 (0.13)</td>
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<td>NR</td>
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<td></td>
<td></td>
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<td>55/45</td>
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<td></td>
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<td>12</td>
<td>20</td>
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<td>14 (44)</td>
<td>63/38</td>
<td>NR</td>
<td>2.2 (0.12)</td>
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<tr>
<td>Kellar</td>
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<td>13</td>
<td>7</td>
<td>NR</td>
<td>17.2 (4.28)</td>
<td>15 (75)</td>
<td>5/15</td>
<td>NR</td>
<td>24.13 (6.46)</td>
<td>43.25 (7.89)</td>
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<td></td>
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<td>Insulin</td>
<td>18</td>
<td>69.94 (6.12)</td>
<td>10</td>
<td>8</td>
<td>NR</td>
<td>16.05 (2.87)</td>
<td>14 (78)</td>
<td>8/10</td>
<td>NR</td>
<td>25.11 (9.17)</td>
<td>38.89 (7.36)</td>
<td>NR</td>
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<tr>
<td>Reger</td>
<td>2008</td>
<td>Normal E4−</td>
<td>48</td>
<td>73.8 (1)</td>
<td>26.1 (0.6)</td>
<td>14.6 (0.4)</td>
<td>48 (52)</td>
<td>20/13</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td>Normal E4+</td>
<td>11</td>
<td>72.5 (2)</td>
<td>25.6 (1.2)</td>
<td>15.2 (0.8)</td>
<td>11 (12)</td>
<td>20/13</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
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<td>11</td>
<td>76.3 (2)</td>
<td>26.4 (1.2)</td>
<td>14.5 (0.8)</td>
<td>11 (12)</td>
<td>20/13</td>
<td>NR</td>
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<td></td>
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<td></td>
<td></td>
<td>22 (24)</td>
<td>20/13</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
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<td>Normal E4− (2006) [19]</td>
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<td>Normal E4+</td>
<td>8</td>
<td>73</td>
<td>25.9</td>
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<tr>
<td>MCI E4−</td>
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<td>76.8</td>
<td>24</td>
<td>4</td>
<td>14 (3.2)</td>
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<td>13/13</td>
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<td>4</td>
<td>13.8 (3.6)</td>
<td>NR</td>
<td>13/13</td>
<td>NR</td>
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<td>25.2</td>
<td>2</td>
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<tr>
<td>AD E4+</td>
<td>7</td>
<td>76.6</td>
<td>25.4</td>
<td>3</td>
<td>15.7 (2.1)</td>
<td>NR</td>
<td>13/13</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td></td>
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<tr>
<td>Placebo (2007) [17]</td>
<td>Reger</td>
<td>12</td>
<td>79.3</td>
<td>26</td>
<td>15.5 (0.9)</td>
<td>NR</td>
<td>14/11</td>
<td>NR</td>
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<td>NR</td>
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<tr>
<td>insulin</td>
<td>13</td>
<td>77.1</td>
<td>26.9</td>
<td>14</td>
<td>14.9 (0.8)</td>
<td>NR</td>
<td>14/11</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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**Abbreviation:**
Apo e4, Apolipoprotein E4; DRS, Dementia Severity Rating Scale; ADAS-cog, Alzheimer Disease’s Assessment Scale—cognitive subscale; ADCS-ADL, Alzheimer’s Disease Cooperative Study–activities of daily living; CDR-SOB Clinical Dimension Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; NR, not reported
3.3.3. Memory composite (delayed story recall) 40 IU

We pooled the four studies that provided relevant data for memory composite 40IU involving 400 participants. The overall effect did not favor either of the two groups in terms of memory composite 40IU. The MD was 0.25 (95% CI -0.09 to 0.6, P = 0.15). The results were homogenous (I² = 0%, P = 0.99) **Figure 3C**.

3.3.4. Memory composite (delayed story recall) 20 IU

Two studies reported relevant data for memory composite 20IU involving a total of 132 participants. There was no significant difference between the intranasal insulin and the placebo. The MD was 0.65 (95% CI -0.08 to 1.39, P = 0.08). The pooled studies were homogenous (I² = 0%, P = 0.51), **Figure 3D**.

3.3.5. Memory composite (delayed story recall) Long-Acting

Two studies provided adequate data for memory composite long-acting involving 63 participants. We found no significant difference between the intranasal insulin and the placebo. The MD was 0.58 (95% CI -0.04 to 1.19, P = 0.07). The results were homogenous (I² = 0%, P = 0.71), **Figure 3E**.

3.3.6. DSRS 40IU

Three studies reported relevant data for DSRS 40 IU with a total of 160 participants. The overall effect did not favor either of the two groups in terms of DSRS 40 IU. The MD was -0.15 (95% CI -0.88 to 0.57, P = 0.68). The findings of the studies were homogenous (I² = 0%, P = 0.6), **Figure 3F**.
Figure 3. Forest plots of mean difference in (A) ADAS-cog 40IU, (B) ADAS-cog 20IU, (C) Memory composite 40IU, (D) Memory composite 20IU, (E) Memory composite long-acting and (F) DSRS 40IU.
3.3.7. DSRS 20IU

Regarding DSRS 20 IU, we identified two relevant studies with a total of 132 participants. There was no significant difference between the two groups. The MD was -0.11 (95% CI -0.82 to 0.6, P = 0.76). The pooled articles were homogenous (I² = 0%, P = 0.59), **Figure 4A**.

3.3.8. DSRS-LA

Two studies provided relevant data for DSRS-LA with a total of 63 participants. The overall effect did not favor either of the two groups in terms of DSRS-LA. The MD was 0.16 (95% CI -3.98 to 4.29, P = 0.94). The results were homogenous (I² = 0%, P = 0.85), **Figure 4B**.

3.3.9. ADCS-ADL 40 IU

We identified three studies that reported relevant data for ADCS-ADL 40 IU involving a total of 376 participants. The overall effect did not favor either of the two groups in terms of ADCS-ADL 40IU. The MD was 0.04 (95% CI -0.07 to 0.15, P = 0.49). The pooled studies were homogenous (I² = 0%, P = 0.58), **Figure 4C**.

3.3.10. ADCS-ADL 20 IU

Two studies provided adequate data for ADCS-ADL 20 IU with a total of 132 participants. The overall effect did not favor either of the two groups in terms of ADCS-ADL 20IU. The MD was 0.02 (95% CI -0.09 to 0.13, P = 0.72). The results were homogenous (I² = 0%, P = 0.59), **Figure 4D**.

3.3.11. Clinical Dementia Rating-Sum of Boxes score

Two studies provided relevant data for clinical dimension rating—the sum of boxes involving 268 participants. We did not find a significant difference between the two groups. The MD was 0.36 (95% CI -0.19 to 0.92, P = 0.2). The results were homogenous (I² = 0%, P = 0.54), **Figure 4E**.
Figure 4. Forest plots of mean difference in (A) DSRS 20IU, (B) DSRS-LA, (C) ADCS-ADL 40 IU, (D) ADCS-ADL 20 IU, and (E) Clinical Dementia Rating-Sum of Boxes score.

3.3.12. CSF biomarkers of AD

We found a non-significance difference between the intranasal insulin and the placebo in the case of CSF Biomarkers of AD. The MD was -3.23 (95% CI -9.9 to 3.44, P = 0.34). In addition, the overall
effect did not favor either of the two groups in terms of Abeta42, Tau, and Tau-P. More information is in Figure 5.

### Figure 5

Forest plots of mean difference in CSF Biomarkers of AD.

3.3.13. Adverse effects

We categorized data into three subgroups (Headache, Rhinitis/URI, and Fall) involving 1001 participants. The findings of overall adverse events and the subgroups revealed no significant difference between the two groups. The RR of overall adverse events was 1.28 (95% CI 0.75 to 2.21, \( P = 0.36 \)).

All details are in Figure 6.
4. Discussion

The introduction of effective medicine for several CNS-related disorders, including AD, by nose-to-brain drug administration, has been considered a revolutionary process [21]. Intranasal insulin is one of these treatments that has shown a beneficial impact on AD patients [11]. In the present study, 12 RCTs were included. All the included studies retrieved from our literature search compared intranasal insulin with placebo in terms of safety and efficacy. The duration of treatment in the included studies ranged from four months to four years. The findings of our meta-analysis revealed that intranasal insulin might be significant...
in improving cognition in Alzheimer’s disease patients measured by ADAS-cog with lower doses being more effective. There was no difference in the incidence of adverse effects between both arms which suggests that short-term intranasal insulin could be safe in treating Alzheimer’s disease patients. In addition, CSF biomarkers, clinical dementia rating score, dementia severity rating scale, and memory composite showed no significance in either dose of insulin compared to the placebo.

Generally, ADAS-Cog is a reliable assessment tool for Alzheimer’s disease. It contains items regarding language, memory, praxis, and orientation with higher scores representing greater impairment. These items are beneficial in not only diagnosing Alzheimer’s disease patients from healthy people but also helping in determining the severity of the disease through the items in the orientation section [22]. Also, we need to differentiate between MCI and dementia. MCI is a period between dementia and normal cognitive impairment associated with getting older. There are amnestic and non-amnestic types of it [23]. Dementia is a generic term for a deterioration in cognitive functions that makes it difficult to carry out daily tasks [24]. Once the patient is in the MCI stage, it’s regarded as a major risk of being a dementia patient [23].

Our meta-analysis showed significantly less decline in ADAS-cog score from the baseline in the insulin 20 IU group when compared to the placebo. This is consistent with individual study results which showed that the insulin group had less decline in cognitive function over time when compared to the placebo [9,11,13].

The results did not reach a significant cut-off point when we compared insulin 40 IU and placebo regarding ADAS-cog scores. The findings of the individual studies involved in the analysis varied. Some studies supported our results that 40 IU insulin loses its effect on cognition. A possible explanation of this finding could be attributed to the small sample size, the short duration of the trials which make it difficult to detect significant differences, and the use of unreliable devices or insulin formulations that are not proven to be effective on memory [12,25,26]. Claxton 2013[9] and craft 2017[14] showed a possible correlation between ApoE 4 and the treatment response specific to the 40 IU insulin. Additionally, Claxton 2013[9] demonstrated a gender/ ApoE 4 interaction with a better improvement of cognitive function in ApoE 4 negative males and more decline in ApoE 4 negative females [9,14]. Given our p-value (0.08) and our
confidence interval most of it was in the direction of favoring 40 IU insulin. Further studies with larger sample sizes and longer durations are needed to confirm this association and the efficacy of using the 40 IU insulin in the treatment of Alzheimer’s disease patients.

On the contrary, some studies showed that ADAS-cog score is significantly improved with the administration of 40 IU insulin compared to placebo. Craft 2012 [11] showed a significant difference in ADAS-cog score between 40 IU insulin and placebo [11]. Reger et al demonstrated that the effect of insulin on cognition is dose-dependent and the curve shows a U-shaped pattern, meaning that enhanced cognition can be achieved by optimal dose while the extremes of doses will have less effect. The 40 IU might have exceeded the optimal dose of memory but not for other items of the ADAS-cog score and this explains the significant difference between the placebo in the ADAS-cog score and not in delayed story recall [18]. Another study showed that the insulin signaling pathway is better activated in smaller doses compared to higher doses which can cause insulin resistance and worsen the condition of an already existing memory impairment [27]. Claxton’s 2013 results support this theory as they showed similar results regarding delayed story recall and ADAS-cog score [9].

We found that there was a non-significant difference between 20 IU insulin and placebo regarding delayed story recall. Craft 2012 reported a significantly better story recall compared to a placebo [11]. This could be attributed to the imprecision and wide confidence interval observed in Claxton 2013 [9]. When we compared 40 IU insulin with a placebo, there was no significant difference in story recall between both groups. This is consistent with the results of individual studies and could be explained by the U-shaped dose-dependent theory that was mentioned above. This means that 40 IU insulin might have exceeded the optimal dose for memory composite.

The ADCS-ADL is a scale used to measure the capability of AD patients to perform daily activities with higher scores indicating better preservation of functional capacity [9]. Our results showed that there’s no difference in ADCS-ADL between both insulin groups and the placebo. This is consistent with the findings of two of the included studies which reported this outcome. However, Claxton 2013 showed a difference
in ADCS-ADL between males and females in favour of females [9]. Moreover, Craft 2012 showed that there’s a significant difference between the insulin and placebo group for Alzheimer’s disease but not for amnestic mild cognitive impairment (aMCI) [11].

The DSRS is a similar scale to ADCS-ADL determined by a questionnaire that contains questions about the cognitive, functional, and social status of the patient. Higher scores indicate greater impairment. Our results found no significant difference between the low dose of insulin and the placebo group. Craft 2012 reported similar results at 6 months of evaluation [11]. However, significant improvement in DSRS at 2 months was observed. Moreover, Claxton 2013 endpoint at 4 months revealed marginal significance in DSRS between placebo and 20 IU insulin [9]. This could be due to a time-dependent relation which suggests that 20 IU insulin might be beneficial in the short term and relatively loses its benefits onwards. Regarding 40 IU or long-acting insulin, our results as well as the results of the individual studies showed no difference with the placebo irrespective of the time of assessment.

In the context of the main pathophysiological changes in AD patients, Beta peptides, Tau protein, and Tau-p protein are known to play the main role in AD pathology. Insulin was thought to protect against amyloid-beta peptides and reduce tau phosphorylation [28–30]. However, the limited insulin transport across the BBB reduces this protective effect [31]. The intranasal administration of insulin was a new route to bypass the BBB as insulin travels along perivascular pathways following olfactory and trigeminal nerves [32].

In our study, we assessed the effect of intranasal insulin administration on the levels of the three biomarkers A beta, tau, and tau-p in the CSF. We found no significant difference in any of the three biomarkers between insulin and placebo. Although this is consistent with the individual study results, exploratory analysis of one study showed that increased levels of amyloid-beta concentration and decreased tau protein–to–AB 42 ratio were associated with improved delayed story recall and daily function. This association was only found in the insulin group. Thus, such results couldn’t be attributed to disease progression status. Moreover, selection bias could have happened since not all participants underwent lumbar punctures [11]. However,
additional studies with larger sample sizes are needed to further examine the effect of intranasal insulin on Alzheimer’s disease pathology.

In the assessment of intranasal insulin safety, our meta-analysis showed no significant difference in the incidence of complications in the insulin group compared to the placebo group. The included studies reported no serious adverse effects, and the complications were limited to minor complications such as upper respiratory symptoms and rhinitis. Apart from a higher rate of nasal irritation reported in Rosenbloom and a higher total number of minor adverse events reported in craft 2012, the overall results showed no significant difference in the incidence of complications between insulin and placebo groups [11,12]. Moreover, these studies reported good compliance which wasn’t different between the two arms [11,12,14]. Thus, weighing the risk-benefit ratio of this treatment, intranasal insulin could be a safe therapy for Alzheimer’s disease patients. Rosenbloom included non-insulin-dependent diabetic patients who reported that they well tolerated the treatment with no major adverse effects or hypoglycemia. However, these studies were done over a short duration, making their long-term safety and efficacy inconclusive. Thus, larger sample sizes and longer-duration clinical trials are needed to assess the long-term benefits of intranasal insulin and the correlation between patients’ characteristics and their response to treatment.

In the latest network meta-analysis [33]. They evaluated the efficacy of 6 different antidiabetic drugs, including intranasal insulin 40 IU and 20 IU. No discernable difference was found when assessing the acceptability of the agents (defined by all-cause discontinuation). Additionally, Cognitive assessment using ADAS-Cog showed no significant improvement in either dose (20 IU or 40 IU) compared with the placebo. Nonetheless, our study found that intranasal insulin delivered at 20 IU improved the ADAS-Cog, but not at 40 IU. This cognitive change in response to low-dosage intranasal insulin was related to neuronal extracellular vesicles (EV) biomarkers of insulin resistance (pS312-IRS-1, pY-IRS-1), suggesting activation of the insulin signaling cascade at the IRS-1 level.
4.1. Limitations and strengths of the study

The major limitation of this study included: the inability to perform a meta-analysis of five of the included studies due to several variations between these articles, such as reporting different outcomes utilizing various scores and some discrepancies in the duration of intervention. Future research is warranted to explore the efficacy of intranasal insulin in a larger sample with longer follow-ups, taking into consideration the apoE4 status and the progressive neurodegeneration that occurs over many years and needed longer duration studies.

Nevertheless, the strengths of our study are as follows: (1) our meta-analysis represented the last updated evidence assessing the efficacy and safety of intranasal insulin in patients with AD, (2) we provided a more comprehensive analysis in an attempt to solve the previous conflicting findings, (3) we complied the PRISMA checklist when representing this manuscript and conducted all steps as stated in the Cochrane Handbook in our review.

Conclusion

Ultimately, the current results of intranasal insulin are encouraging in terms of safety and efficacy. Our findings demonstrate that the administration of lower doses (20 IU) has distinctly more efficacy than higher doses (40 IU) as revealed by the ADAS-cog scale. To learn about the variations (sex, age, and ApoE4 carriage) in treatment responses and make the most of this intervention, further trials are required. Additionally, a future investigation should require reliable insulin delivery devices with proven capacity to increase insulin in the central nervous system.

Conflict of interest

All authors have no conflict of interest.
References


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