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REVIEW

Intranasal insulin in Alzheimer's dementia or mild cognitive impairment: a systematic review

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Abstract

Background and aims Due to common pathophysiological findings of Alzheimer's disease (AD) with diabetes mellitus (DM), insulin has been suggested as a possible treatment of AD or mild cognitive impairment (MCI). A safe alternative of IV insulin is intranasal (IN) insulin. The aim of this systematic review is to investigate the effects of IN insulin on cognitive function of patients with either AD or MCI.

Methods A literature search of the electronic databases Medline, Scopus and CENTRAL was performed to identify RCTs investigating the effect of IN insulin administration on cognitive tasks, in patients with AD or MCI.

Results Seven studies (293 patients) met our inclusion criteria. Most studies showed that verbal memory and especially story recall was improved after IN insulin administration. Sometimes the effect was restricted for apoe4 (−) patients. Intranasal insulin did not affect other cognitive functions. However, there were some positive results in functional status and daily activity. Data suggested that different insulin types and doses may have different effects on different apoe4 groups. In addition, the effects of treatment on Aβ levels differed from study to study. Finally, IN insulin resulted in minor adverse effects.

Conclusions Intranasal insulin improved story recall performance of apoe4 (−) patients with AD or MCI. Other cognitive functions were not affected, but there were some positive results in functional status and daily activity. Since IN insulin is a safe intervention, future studies should be conducted with larger doses and after proper selection of patients and insulin types.

Keywords Alzheimer's disease · MCI (mild cognitive impairment) · Cognitive function · Intranasal insulin · Systematic review

Introduction

Alois Alzheimer described the first case of what would be defined as Alzheimer's Disease (AD) over 100 years ago [1]. Recent studies have shown that the overall point prevalence of dementia due to AD among individuals older than 60 years is over 40 per 1000 persons [2]. The disease affects society both in terms of economy and of quality of life [3]. Despite the use of many different treatments, there

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is currently no effective way to halt the progression of the disease [4–8].

Diabetes mellitus (DM) is a risk factor for vascular dementia, as well as AD [9]. Moreover, the incidence of any type of dementia, including that of AD, is higher among people with DM [10, 11]. AD shares common pathophysiological abnormalities with DM, among which is insulin resistance and amyloidogenesis [12]. Due to these neuroendocrine abnormalities, AD has been characterized as "type 3 diabetes" [13]. Beta-amyloid, which is the hallmark pathologic characteristic of AD has been implicated in synapse toxicity and hippocampal neuronal damage and consequently in cognitive and memory impairment; intravenous administration of insulin alleviates these pathophysiologic effects [14, 15]. It has also previously been shown, that intravenous (IV) insulin administration improves memory in AD [16, 17]. However, the systemic side effects of IV insulin, mainly hypoglycemia, limit the safety and feasibility of this administration route. Intranasal (IN) insulin administration is a non-invasive method which delivers insulin to the brain parenchyma very rapidly and effectively, reaching cerebral concentrations 100-fold higher than intravenous delivery, bypassing the blood–brain barrier via paracellular transport [18–20]. IN insulin has negligible risk of systemic hypoglycemia and its potential as treatment agent in AD has been explored in clinical studies [19, 21, 22]. Furthermore, MCI is a condition that many times evolves to AD [23]. In addition, there is no current treatment for MCI, so treatment with IN insulin can involve this group of patients, too [23].

We undertook the present systematic review of randomized clinical trials, evaluating the potential beneficial effects of IN insulin on patients with either AD or mild cognitive impairment (MCI) [23]. Our primary goal was to investigate whether existing data support the use of IN insulin as a treatment option in MCI or Alzheimer's dementia.

Methods

Protocol and registration

The protocol of our systematic review was prospectively registered on PROSPERO and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016051385. We adopted the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [24].

Eligibility criteria

We included studies according to the following eligibility criteria: (a) Double blind randomized control trials or double blind randomized cross-over studies. (b) Published in the English language up to 10/14/2017. (c) Reporting findings in humans. (d) Patients with diagnosis of either MCI or AD. (e) Patients were treated with intranasal insulin or placebo. (f) Patients were tested on memory or other cognitive domains with the use of various different assessment tools.

Information sources

Medline, Scopus and Cochrane Central Register of Controlled trials were searched for relevant published studies up to 10/14/2017.

Search

In the above databases we used the following search query: "(Intranasal insulin OR nasal insulin) AND (Alzheimer's dementia OR Alzheimer's disease OR Alzheimer's OR neurodegenerative disease OR cognitive impairment OR neuroprotective OR memory OR cognition)".

Study selection

For identification of eligible studies, two reviewers (GK, AM) searched independently, based on the inclusion criteria. Any disagreement was solved with the contribution of a third reviewer (PM) and consensus.

Data collection process and data items

Data were extracted by two reviewers (GK, AM) independently and included the following fields: Title, first author, ID, year of publication, journal, country of origin, study type, study duration, total number of participants, number of patients that assigned IN insulin and placebo, type of IN insulin administered, baseline characteristics of participants, apoe4 gene carriage status, CSF and plasma Aβ amyloid levels, primary outcomes (verbal memory, attention, executive function, response inhibition, visuospatial function, functional status, daily activity and general cognition after treatment) and secondary outcomes (adverse effects and levels of insulin, glucose and plasma Aβ amyloid after treatment).

Risk of bias in individual studies

Risk of bias in randomized control trials was assessed by 2 reviewers (DK and PM) independently using the Cochrane Collaboration's tool for assessing risk of bias (ROB) [25]. The evaluation was performed for every outcome within each study. Disagreements between authors were solved through consensus. The domains assessed were bias due to random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection

bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). A study was characterized of high risk for overall ROB if at least one ROB domain was of high risk. All ROB domains had to be of low risk for a study to be characterized as of low risk. In any other case, the study was deemed to be at unclear overall risk. Regarding the Rosenbloom et al. study, due to the cross-over design, risk of bias was based on the instructions of Cochrane Handbook for Systematic Reviews of Interventions for cross-over trials.

Results

Search results

The search yielded 306 potentially eligible studies. After duplicates were removed, 186 articles were excluded based on their title and abstract. Eventually, 12 full-text articles were assessed for eligibility. Three articles were excluded because they were conference abstracts and contained incomplete information or potential duplicate results [26–28]. Another study was excluded as it was not an RCT [13]. Finally, one study was excluded because it did not provide enough statistical data [29]. The flowchart presenting the selection of studies is provided in Fig. 1.

Studies' and patients' characteristics

Seven articles were eventually deemed eligible, including a total of 293 patients [30–36]; 172 were diagnosed with MCI and 121 with AD. The patients were assigned either to IN insulin or placebo group. Four studies assessed the effect of IN regular insulin [31–34]. In two studies IN insulin glulisine and detemir were administrated, respectively [30, 35]. In another study, both IN regular and detemir were used [36]. Three studies examined the cognitive effects of IN insulin acutely after treatment [32, 33, 35]. In the rest of the studies, cognitive tasks were applied after a long period of treatment [30, 31, 34, 36]. The treatment doses varied from study to study. In addition, the patients' apoe4 gene carriage status varied from study to study. The studies' and patients' characteristics are summarized in Tables 1 and 2, respectively.

Risk of bias

Regarding assessment of ROB, none of the randomized control trials (RCTs) was judged as of high risk. One study was deemed to be at low ROB [33]. Most studies were characterized of unclear ROB due to unclear risks in "allocation concealment" and/or "blinding of participants and personnel" and/or "blinding of outcome assessment" domains [30–33, 36]. Details about ROB assessment are presented in Figs. 2 and 3. Rosenbloom et al. cross-over study was judged as of low risk because the cross-over design was suitable for this trial (AD is a reasonably stable condition), the order of receiving treatments was randomized and there were no carry-over treatment effects.

Results of individual studies

Primary outcome (cognitive tasks)

Verbal memory and verbal working memory

Verbal memory was tested in all included studies with the assessment of the story recall task and the word list recall task [30–36]. Verbal working memory was tested only in one study, with the DOT counting N-back test [30].

Sometimes, response to treatment differed according to apoe4 status [32, 33]. One study showed that compared with placebo, various IN insulin doses (10, 20, 40 IU) improved immediate recall in apoe4 (−) and worsened it in apoe4 (+) patients, respectively [33]. Again, after administration of same insulin doses, delayed recall performance had a trend towards worsening among apoe4 (+), whereas it was unaffected among apoe4 (−) patients [33]. In another study, when compared with placebo, 20 and 40 IU of IN insulin significantly improved performance on the composite score of immediate and delayed story recall, in apoe4 (−) patients but no changes were observed for apoe4 (+) patients [32].

In two studies, story recall improved after administration of 20 and 40 IU of IN insulin, but patients were not stratified according to apoe4 status [31, 34]. In another study, in which 20 IU of IN insulin was given, performance on story recall was not affected but patients were solely apoe4 (+) [35].

Performance on immediate and delayed word list recall was either not affected or the results were conflicting [32, 33, 35]. One study assessed verbal memory as a composite score of immediate story recall, delayed story recall, immediate word list recall and delayed word list recall [30]. Score worsened for apoe4 (−) and improved for apoe4 (+) patients [30]. However, a long-acting form of insulin was used in this study (detemir) as opposed to regular insulin which is short-acting [30]. In another study, a composite score of delayed story recall and delayed word list recall was used [36]. This was the only study to implement two types of IN insulin (regular, detemir) for comparison with placebo [36]. Intranasal regular insulin was beneficial for apoe4 (−), while IN detemir improved performance in apoe4 (+) patients.

Verbal working memory was assessed only in one study [30]. Performance was improved after the 40 but not the 20 IU dose, regardless of apoe4 status [30]. The effects of IN insulin on verbal memory are presented in Table 3.

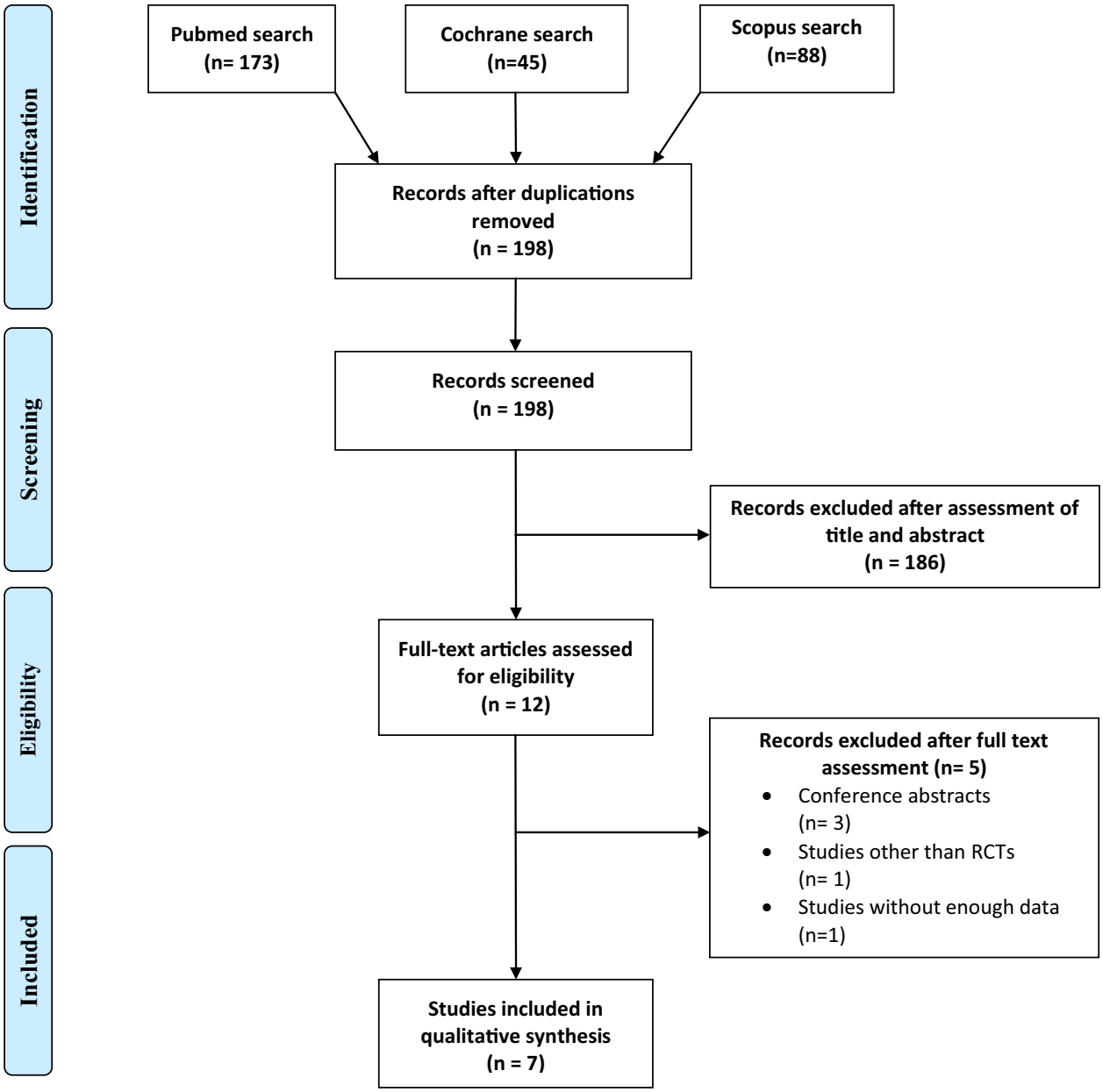

Fig. 1 Flow diagram

Attention, executive function and response inhibition

Attention, executive function and response inhibition were tested in five studies [30, 32–35]. In four of them, the assessment of attention and response inhibition was done with SCWT (Stroop Color Word Test) [30, 32–34]. In general, no significant effects were observed in SCWT after administration of different types and doses of intranasal insulin [30, 32–35]. Significant improvement was noticed only in one study, but the effect was restricted to discordant items [34]. There was no effect on concordant items or the number of errors [34].

Another study assessed attention/executive function with the use of "Trails B test", "RBANS digit span forward" and "RBANS digit span backward" [35]. Significantly improved performance was observed only for the first task [35] (Table 4).

Table 1 Characteristics of included studies

First author and year	Country	Study type	Treatment duration (days)	Number of patients (total/MCI/AD)	Type of IN insulin given	IN insulin dosages (IU)
Reger [32]	USA	RCT	Short term (1)	26/13/13	Regular	20/40
Reger [34]	USA	RCT	Long term (21)	25/14/11	Regular	20
Reger [33]	USA	RCT	Short term (1)	33/20/13	Regular	10/20/40/60
Craft [31]	USA	RCT	Long term (120)	104/64/40	Regular	20/40
Rosenbloom [35]	USA	Cross - over RCT	Short term (1)	9/0/9	Glulisine	20
Claxton [30]	USA	RCT	Long term (21)	60/39/21	Detemir	20/40
Craft [36]	USA	RCT	Long term (120)	36/22/14	Regular/Detemir	40

RCT randomized clinical trial, *MCI* mild cognitive impairment, *AD* Alzheimer's disease, *IN* intranasal, *Regular insulin* a short acting type of insulin, *Glulisine* a rapid acting insulin analogue, *Detemir* a long-acting insulin analogue

Table 2 Demographic characteristics of patients in each study

First author and year	Apo e4 status (±)	Gender (f/m)	Age (years)	BMI (kg/m^2)	Education (years)
Reger [32]	12/14	13/13	76.7 (5.5)	24.7 (2.8)	14.3 (3.2)
Reger [34]	NR	NR	78.2 (1.6)	26.5 (1.2)	15.2 (0.8)
Reger [33]	11/22	NR	76.6 (1.6)	26.6 (0.9)	14.6 (0.7)
Craft [31]	57/47	45/59	68.9 (1.5)	27 (0.8)	15.7 (0.5)
Rosenbloom [35]	0/9	0/9	72 (65–85)	NR	NR
Claxton [30]	NR	NR	NR	NR	NR
Craft 2017 [36]	14/22	17/17	68.7 (8.6)	28.3 (5.3)	15.6 (2.4)

NR not reported

In Craft et al.: age, BMI and education were expressed as mean (SEM)

In Rosenbloom et al.: age was expressed as mean (range)

In rest of the studies: age, BMI and education were expressed as mean (SD)

In Claxton et al.: age, BMI and education were not reported. However, it was stated that placebo did not differ from treatment group

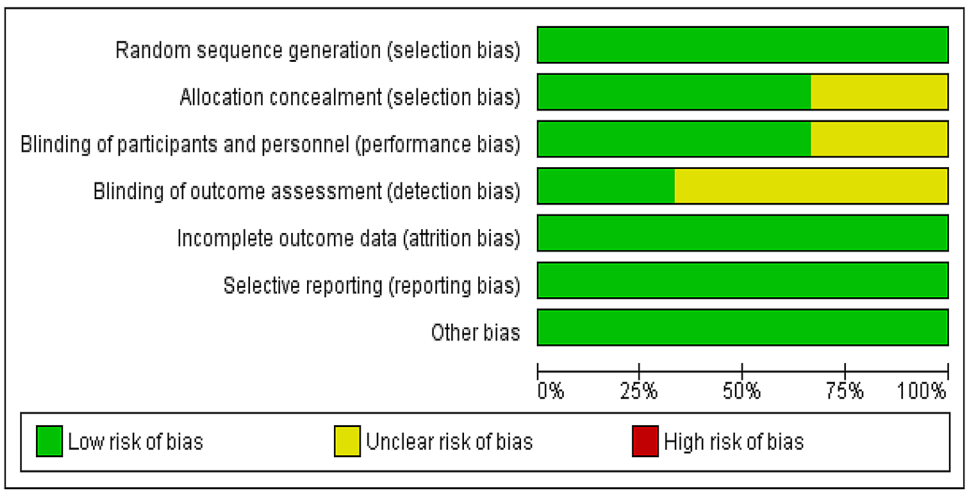

Fig. 2 Risk of bias graph authors' judgements about each risk of bias item, presented as percentage across all included studies

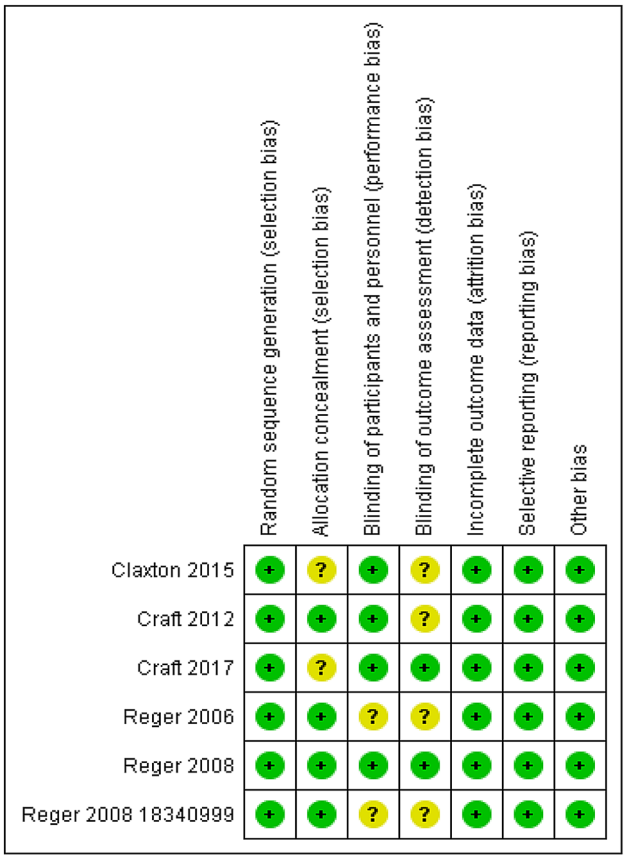

Fig. 3 Risk of bias summary

Visuospatial function

Visuospatial function was assessed in four studies [30, 32, 33, 35]. In general, no significant effects were observed [30, 32, 33, 35]. Exception to this was the significantly improved performance regardless of apoe4 status on BVTR (Benton Visual Retention Test) after the administration of 40 IU of IN insulin detemir, regardless of apoe4 status [30]. The effect was not observed for the 20 IU dose [30] (Table 5).

Functional status, daily activity and global cognition

Functional status and daily activity were assessed in four studies with the use of DSRS (Dementia Severity Rating Scale) or Alzheimer's Disease Cooperative Study-activities of daily living (ADCS-ADL) scores, respectively [30, 31, 34, 36]. Regarding DSRS scores, the results were conflicting [30, 31, 34, 36]. ADCS-ADL scale scores were preserved for AD patients of the insulin-assigned group but declined for the AD patients of the placebo group; scores of MCI patients were all unaffected regardless of group assignment [31]. Craft et al. used a measure of global cognition named ADAS-Cog scale, in their two studies [31, 36]. Improvements were found only in one study [31] (Table 6).

Secondary outcomes

Effects on Aβ40 and Aβ42

Two studies reported the effects of IN insulin on plasma Aβ40 and Aβ42 amyloid levels [33, 34]. In addition, two studies reported the effects on the CSF Aβ40 and Aβ42 levels [31, 36]. The results were very conflicting [31, 33, 34, 36] (Table 7).

Metabolic data

Four studies reported the effects of IN insulin treatment on plasma glucose and insulin levels [32–35]. In three of them, no significant change in plasma glucose or insulin levels were observed after treatment [32, 33, 35]. In Rosenbloom et al.'s study, there was also no change in fasting glucose or insulin levels after 21 days of treatment [35]. However, reduced postprandial plasma insulin levels were observed for treatment group when compared to placebo [$F(1, 20 = 4.43$, $p = 0.0481)$] [35].

Adverse effects

Adverse effects included nose-related side effects (minor bleeding, soreness, rhinitis, sneezing), headache, dizziness, weakness and upper respiratory tract infections. A complete list of adverse effects is depicted in Table 8.

Discussion

In this systematic review of randomized clinical trials, we found evidence that IN insulin may have a beneficial effect on verbal memory, probably modified by apoe4 allele carrier status; the effect was favorable for apoe4 (−) patients but not for apoe4 (+) patients. For the rest cognitive domains (visuospatial function, attention, executive function, response inhibition and everyday functioning) there was not any clear effect by IN insulin administration. Of note, the expected absence of systemic side effects of IN insulin treatment was confirmed by our findings.

Response to treatment and apoe4 status

Of all cognitive domains tested, verbal memory (story and/or word list recall) was affected the most. Interestingly, the patients' apoe4 allele carrier status appeared to determine the response to treatment, which is in accordance with

Table 3 Effects of IN insulin on verbal memory

Dose (IU), type of IN insulin	Duration of intervention (days)	Study (1st author, year)	Cognitive task	Main findings
10 IU Regular	Short (1)	Reger [33]	(i) Story recall	Improved memory for apoe4 (−) in comparison to worsened memory for apoe4 (+) [$p = 0.0484$]
			(d) story recall	Unchanged memory for apoe4 (−) in comparison to apoe4 (+) whose performance had a worsening trend [$p = 0.1061$]
			(i) word list recall	Reduced memory for apoe4 (−) and apoe4 (+), no significant difference between the two groups
			(d) word list recall	Improved memory for apoe4 (−) and reduced memory for apoe4 (+), no significant difference between the two groups
20 IU Regular	Short (1)	Reger [32]	(i) + (d) story recall	Significant memory improvement for apoe4 (−) [$p = 0.00006$]. No significant change for apoe4 (+)
			(i) + (d) word list recall	No change in memory for any apoe4 group
	Short (1)	Reger [33]	(i) story recall	
			(d) story recall	Unchanged memory for apoe4 (−) in comparison to apoe4 (+) whose performance had a worsening trend [$p = 0.0739$]
			(i) word list recall	Improved memory for both apoe4 (−) and apoe4 (+), with a trend of significant improvement for apoe4 (−) in comparison to apoe4 (+) [$p = 0.0637$]
			(d) word list recall	
	long (21)	Reger [34]	(i) + (d) story recall	Significant memory improvement of insulin treated relative to placebo ($p = 0.0374$). *Limitation* no apoe4 groups reported
	long (120)	Craft [31]	(d) story recall	Improved memory (treatment group × time interaction: $p = 0.02$, Cohen $f = 0.36$). *Limitation* no apoe4 groups reported
20 IU Glulisine	Short (1)	Rosenbloom [35]	(i) + (d) story recall	No change in memory
			(i) + (d) list recall	No change in memory *Note* all patients finally analyzed, were apoe4 (+) and males
20 IU Detemir	Long (21)	Claxton [30]	Sum of [(i) + (d) story recall] +[(i) + (d) word list recall]	No change in memory for both apoe4 groups
			Dot counting N back	No change in memory. *Limitation* no apoe4 groups reported
40 IU Regular	Short (1)	Reger [32]	Sum of (i) + (d) story recall	Significant memory improvement for apoe4 (−) [$p = 0.0013$]. No significant change for apoe4 (+)
			Sum of (i) + (d) word list recall	Significant memory improvement for the apoe4 (−) [$p = 0.0323$]. Significant worsening for the apoe4 (+) [$p = 0.0044$]
	Short (1)	Reger [33]	(i) Story recall	Improved memory for apoe4 (−) in comparison to worsened memory for apoe4 (+) [$p = 0.0273$]

Table 3 (continued)

Dose (IU), type of IN insulin	Duration of intervention (days)	Study (1st author, year)	Cognitive task	Main findings
			(d) story recall	Unchanged memory for apoe4 (−) in comparison to apoe4 (+) whose performance had a worsening trend [$p = 0.0595$]
			(i) word list recall	Reduced memory for both apoe4 (−) and apoe4 (+), no significant difference between the two groups
			(d) word list recall	Reduced memory for apoe4 (−) and improved for apoe4 (+), no significant difference between the two group performance
	Long (120)	Craft [31]	(d) story recall	Unchanged memory. *Limitation* no apoe4 groups reported
	Long (120)	Craft [36]	Sum of (d) story recall + (d) word list recall	Improved memory for apoe4 (−) relative to apoe4 (+) at both 2 and 4 months of treatment (ps < 0.05)
40 IU Detemir	Long (21)	Claxton [30]	Sum of [(i) + (d) story recall] + [(i) + (d) word list recall]	Reduced memory for apoe4 (−) [$p = 0.02$], improved memory for apoe4 (+) [$p = 0.02$]
			Dot counting N back	Improved memory ($p = 0.03$). *Limitation* no apoe4 groups reported
	Long (120)	Craft [36]	Sum of (d) story recall + (d) word list recall	Improved memory for apoe4 (+) compared to placebo, after 2 months of treatment ($p = 0.04$) but no change at 4 months Unchanged memory for apoe4 (−) at 2 and 4 months of treatment
60 IU Regular	Short (1)	Reger [33]	(i) Story recall	Reduced memory for apoe4 (−) and apoe4 (+), no significant difference between the two groups
			(d) story recall	Reduced memory for apoe4 (−) and apoe4 (+), no significant difference between the two groups
			(i) word list recall	Reduced memory for apoe4 (−), improved for apoe4 (+), no significant difference between the two groups
			(d) word list recall	Reduced memory for both apoe4 (−) and apoe4 (+), no significant difference between the two groups

(i) immediate, *(d)* delayed

previous studies [37]. In particular, apoe4 (−) patients were positively affected by treatment especially when they were tested on story recall component of verbal memory [32, 33, 36]. On the other hand, patients with apoe4 (+) status, had either unchanged or worse performance on verbal memory tasks after treatment [32, 33, 35]. Negative for apoe4 gene, AD patients are known to have increased insulin resistance and decreased glucose utilization, in comparison to apoe4 (+) patients [38]. Apolipoprotein4 (−) patients require higher insulin doses than for apoe4 (+) patients, for memory enhancement [37]. However, they have greater memory improvements in hyperinsulinemic states and this may partially explain the selective positive response of apoe4 (−) patients to IN insulin [39]. Our data showed that IN insulin doses of 10 or 20 IU were potent enough to facilitate verbal memory and especially story recall component [31–34]. Generally, absence of apoe4 gene in AD or MCI patients is associated with better responses to various AD treatments, especially in high doses [40–42]. In contrast to apoe4 (−) patients, it is hypothesized that insulin may worsen functional and metabolic brain abnormalities that apoe4 (+) patients are shown to have [43, 44]. In addition, there is evidence of mitochondrial dysfunction in posterior cingulate gyrus of apoe4 (+) carriers [45]. Such a finding

Table 4 Effects of IN insulin on attention, executive function and response inhibition

Dose (IU), type of IN insulin	Duration of intervention (days)	Study (1st author, month)	Cognitive task	Main findings
10 IU Regular	Short (1)	Reger [33]	SCWT	No significant change in performance for any apoe4 group
20 IU Regular	Short (1)	Reger [32]	SCWT	No significant change in performance for any apoe4 group
	Short (1)	Reger [33]	SCWT	No significant change in performance for any apoe4 group
	long (21)	Reger [34]	SCWT	Improved average performance on the selective attention test. The effect was restricted for discordant items ($p = 0.0108$). No change in performance for concordant items (0.9836) or in error number ($p = 0.8383$) *Limitation* no apoe4 groups reported
20 IU Glulisine	Short (1)	Rosenbloom [35]	Trails B test	Fewer errors ($p < 0.05$)
			RBANS digit span forward	No effect on digit span forward ($p = 0.35$)
			RBANS digit span backward	Trend toward worsening performance ($p = 0.051$) on digit span backward
				Note All patients were apoe4 (+)
20 IU Detemir	Long (21)	Claxton [30]	SCWT	No effect for any apoe4 group
40 IU Regular	Short (1)	Reger [32]	SCWT	No change in performance for any apoe4 group
	Short (1)	Reger [33]	SCWT	No significant change in performance for any apoe4 group
40 IU Detemir	Long (21)	Claxton [30]	SCWT	No change in performance for any apoe4 group
60 IU Regular	Short (1)	Reger [33]	SCWT	No significant change in performance for any apoe4 group

SCWT Stroop Color Word Test

could explain the unresponsiveness of apoe4 (+) patients to IN insulin. Studies have demonstrated a relative increase in apoe4 carriage among individuals with AD [46]. These facts may restrict IN therapy application and may at least require appropriate selection of candidates for treatment. However, in two included studies in which a long-acting IN insulin (detemir) was used, there was an improvement for apoe4 carriers in verbal memory, but not for apoe4 (−) [30, 36]. This evidence provides hope for the treatment of apoe4 (+) patients and it could mean that different types of IN insulin are required for different apoe4 groups.

Performance in cognitive domains such as visuospatial function, attention, executive function and response inhibition stayed unaffected [30–35]. One possible explanation is that since these functions have already declined up to some point in AD or MCI patients, the neuropsychological tests may not be sensitive enough to show further decline (or improvement).

Intranasal insulin had some beneficial effects on general functioning of MI patients, tested with DSRS [30, 31, 34, 36]. Regarding ADCS-ADL scale, a daily activity testing tool, there was a beneficial effect for AD patients only, who preserved their function relative to placebo. The same was not true for MCI patients [31, 33, 34]. This may be attributed to the fact that ADCS-ADL scale was originally designed for AD patients only, which are by definition considered to be at a more advanced stage cognitive decline than MCI patients [23]. Finally, performance on a general cognition measure called ADAS-cog varied among studies [31, 36, 47]. Such inconsistencies between studies can be attributed to the small number of subjects participating in those trials [31, 36].

Types and doses of IN insulin

Studies on healthy subjects have shown that IN regular insulin has beneficial effect on memory [48]. Such benefits were shown in our review mostly for story recall task in apoe4 (−) patients, actually for all possible doses (10, 20, 40, 60 IU) and for both short- and long-term treatments [31–34, 36]. It has been suggested that rapid-acting IN insulin is superior to regular insulin [49]. However, this was not confirmed by our included study which used glulisine (rapid-acting insulin) [35]. Of interest, this study included patients that were exclusively apoe4 (+) which is known to be "difficult" for treatment subgroup [45]. This may explain why findings were not in accordance with previous studies [35, 49].

Table 5 Effects of IN insulin on visuospatial function

Dose (IU), type of IN insulin	Duration of intervention (days)	Study (1st author, year)	Cognitive task	Main findings
10 IU Regular	Short (1)	Reger [33]	SOPT	No significant change in performance for any apoe4 group
			Digit symbol	No significant change in performance for any apoe4 group
20 IU Regular	Short (1)	Reger [32]	SOPT	No change in errors for any apoe4 group
			Visual working memory	No change in speed of target identification for any apoe4 group
	Short (1)	Reger [33]	SOPT	No significant change in performance for any apoe4 group
			Digit symbol	No significant change in performance for any apoe4 group
20 IU Glulisine	Short (1)	Rosenbloom [35]	RBANS line orientation	Similar scores for treatment and placebo groups
			RBANS figure copy	No change in performance *Note* All patients finally analyzed were apoe4 (+) and males
20 IU Detemir	Long (21)	Claxton [30]	BVTR (visuospatial working memory)	No effect for any apoe4 group
40 IU Regular	Short (1)	Reger [32]	SOPT	No change in errors for any apoe4 group
			Visual working memory	No change in speed of target identification for any apoe4 group
	Short (1)	Reger [33]	SOPT	No change in performance for any apoe4 group
			Digit symbol	No change in performance for any apoe4 group
40 IU Detemir	Long (21)	Claxton [30]	BVTR (visuospatial working memory)	Improved performance ($p = 0.04$). No interactions with apoe4 status were noticed
60 IU Regular	Short (1)	Reger [33]	SOPT	No change in performance for any apoe4 group
			Digit symbol	No change in performance for any apoe4 group

BVTR Benton Visual Retention Test, *SOPT* Self-Ordered Pointing Task, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status

Despite the unresponsiveness of apoe4 carriers to rapid- or short-acting types of IN insulin (regular, glulisine), there was a beneficial effect after administration of a long-acting IN insulin analogue (detemir) on verbal memory [30, 36]. It is known that insulin detemir binds plasma albumin [50]. In addition, apoe4 carriers with AD have a tendency for post-translational modifications of albumin which in turn may affect the binding of detemir [51, 52]. Thus, special pharmacokinetic properties of insulin determir may be responsible for its positive effects on apoe4 (+) patients. In addition, it has been shown that this type of insulin exerts strong CNS effects which supports further the possible use of it in the resistant to treatment apoe4 (+) patients [53]. Of interest, the benefits were observed for the 40 IU but not the 20 IU dose [30, 36]. This could mean that low doses of detemir may not be enough for improvement of cognitive functions in apoe4 (+) patients, but there is need for further studies to confirm these findings.

Safety issues

Studies on healthy subjects have shown that IN insulin is well tolerated even in high dose (60 IU daily) and for a long period of time (3 weeks) [54]. The observation that serious adverse effects are almost absent after IN insulin administration has already been underlined in previous studies [20, 55]. That was also confirmed by the findings of the present review. The only adverse effects had to do with nasal symptoms, which may be due to the route of administration rather than the drug itself [30–32, 34, 36]. Of great importance is that the risk of hypoglycemia was practically

Table 6 Effects of IN insulin on functional status (DSRS), daily activity (ADCS-ADL) and global cognition (ADAS-Cog)

Dose (IU), type of IN insulin	Duration of intervention (days)	Study (1st year, author)	Cognitive task	Main findings
20 IU Regular	Long (21)	Reger [34]	DSRS	Greater improvement for those with severe impairment at baseline
	Long (120)	Craft [31]	DSRS	Improvement (treatment group × time interaction: $p = 0.01$, Cohen $f = 0.38$)
			ADCS-ADL scale	Overall no improvement. Participants with AD preserved function in comparison to placebo whose function declined ($p = 0.01$, cohen $f = 0.45$) Participants with MCI showed no change
			ADAS-Cog	Less decline in treatment group than placebo group (overall treatment × time interaction. $p = 0.04$, cohen $f = 0.27$) *Note* Patients were mixed apoe4 (±)
20 IU Detemir	Long (21)	Claxton [30]	DSRS	No effect for any apoe4 group
40 IU Regular	Long (120)	Craft [31]	DSRS	Improvement (treatment group × time interaction: $p = 0.01$, Cohen $f = 0.41$)
			ADCS-ADL scale	Overall no improvement. Participants with AD preserved function in comparison to placebo whose function declined ($p = 0.02$, cohen $f = 0.43$). Participants with MCI showed no change
			ADAS-Cog	Less decline in treatment group than placebo group (overall treatment × time interaction. $p = 0.002$, cohen $f = 0.40$) *Note* Patients were mixed apoe4 (±)
			DSRS	No effect for any apoe4 group
	Long (120)	Craft [36]	ADAS-Cog	No effect for any apoe4 group
40 IU Detemir	Long (21)	Claxton [30]	DSRS	No effect for any apoe4 group
	Long (120)	Craft [36]	DSRS	No effect for any apoe4 group
			ADAS-Cog	No effect for any apoe4 group

DSRS Dementia Severity Rating Scale, *ADCS-ADL* Alzheimer's disease Cooperative Study—activities of daily living

negligible, finding that is also in accordance with previous data [30–32, 34, 36, 54]. The minimal risk of hypoglycemia by IN insulin has also been demonstrated in studies where this type of treatment failed to lower glucose in diabetic patients [56–59]. Therefore, IN insulin is a safe treatment for patients with AD or MCI.

Limitations

Intranasal insulin is a novel treatment for patients with AD or MCI and has been only tested in few clinical trials. The present systematic review included a total of 293 patients. Such a small sample size does not allow for safe conclusions. Additionally, all included studies took place at one country (USA), thus there is limitation in generalizability of the results.

Another limitation of the present review is the heterogeneity of the included studies. First of all, there was heterogeneity in respect to patients' characteristics such as gender, age and apoe4 status (see Table 1). In addition, different cognitive domains were assessed in each study, while cognitive tasks varied even among studies assessing the same cognitive domains (see Tables 3, 4, 5, 6). Moreover, types and doses of insulin varied between studies (see Table 1). Finally, the duration of treatment was heterogeneous, too (days of treatment varied from 1 to 120). Consequently, quantitative analysis (meta-analysis) of the included studies was not feasible.

Conclusions

The present systematic review examined the effects of IN insulin administration on cognitive function of patients with AD or MCI. Collective evidence shows improvement in verbal memory and especially story recall, while IN insulin effects on other aspects of cognition was neutral. The data suggest that the treatment effect is modified by the apoe4 gene carriage status of patients: Apoe4 (−) patients showed more consistent cognitive gains in comparison to apoe4 (+) patients, whose performance either remained stable or declined after IN insulin treatment. However, there is evidence hinting that even these patients may benefit from IN insulin if a long-acting form of insulin rather than a rapid or

Table 7 Effects of IN insulin on Aβ

Dose (IU), type of IN insulin	Duration of intervention (days)	Study (1st author, year)	Main findings
10 IU Regular	Short (1)	Reger [33]	Plasma Aβ42 increased significantly regardless of apoe4 status ($p = 0.0213$) No significant change in plasma Aβ40
20 IU Regular	Short (1)	Reger [33]	No significant change in Aβ42 for any apoe4 group No significant change in Aβ40 for any apoe4 group
	Long (21)	Reger [34]	**Fasting levels** No change in Aβ42 ($p = 0.5373$) Increased Aβ40 for treatment group, whereas no change for placebo group [$F_{(1, 22)} = 4.54$, $p = 0.0444$, $f^2 = 0.20$] **Postprandial levels** Decreased Aβ42 in treatment group but same in placebo group [$F_{(1, 22)} = 4.99$, $p = 0.0554$, $f^2 = 0.19$)] Unaffected Aβ40 levels ($p = 0.2076$)
	Long (120)	Craft [31]	No change in Aβ42, Aβ40 of insulin group as a whole
40 IU Regular	Short (1)	Reger [33]	No significant change in Aβ42 for any apoe4 group No significant change in Aβ40 for any apoe4 group
	Long (120)	Craft [31]	No change in CSF Aβ42, Aβ40 of insulin group as a whole
	Long (120)	Craft [36]	No change in CSF Aβ42 for any apoe4 group
40 IU Detemir	Long (120)	Craft [36]	No change in CSF Aβ42 for any apoe4 group
60 IU Regular	Short	Reger [33]	Plasma Aβ42 increased significantly for apoe4 (−) [$p = 0.0071$], but did not change for apoe4 (+) No significant change in Aβ40 for any apoe4 group

Table 8 Adverse effects of IN insulin

Study (1st author, year)	IN insulin group	Placebo group
Reger [32]	1/13 minor nosebleed 1/13 nose soreness for 24 h	None
Reger [33]	NR	NR
Reger [34]	1/13 headache 1/13 nasal dripping 1/13 weakness 1/13 hypoglycemia	No headache 2/13 nasal dripping No weakness 1/13 sneezing
Craft [31]	8/74 lightheadedness or dizziness 6/74 headache 9/74 nosebleed 12/74 rhinitis 3/74 URI 2/74 fall 3/74 rash	3/30 lightheadedness or dizziness 1/30 headache No nosebleed 1/30 rhinitis 1/30 URI 2/30 fall 2/30 rash
Rosenbloom [35]	None	None
Claxton [30]	Some cases of mild rhinitis and dizziness No cases of hypoglycemia	
Craft [36]	7/24 rhinitis 1/12 rhinitis 2/24 headache 0/12 headache 2/24 dizziness 0/12 dizziness 1/24 GI symptoms 1/12 GI symptoms	

NR not reported, *URI* upper respiratory infections, *GI* gastrointestinal

short-acting form is used. Current data are not definite on whether IN insulin can be used as treatment for dementia of AD or MCI but provide strong evidence for its safety as the systemic side effects and especially hypoglycemia were essentially negligible. Proper selection of patients, stratification by disease stage, apoe4 carrier status and different types of insulin and doses will be needed in future studies for clearer results.

Author contributions KLA: Study concept, design and writing of the manuscript (including tables). GK: Data collection process (literature search, flow diagram and data extraction from the included studies). AM: Data collection process (literature search, flow diagram and data extraction from the included studies). DK: Assessment of risk of bias of the included studies (including the respective figures of "Risk of bias"). PM: Contribution to methodology and design of the study, helped with the disagreements of literature search and data extraction which were originally conducted by Dr. Kalaitzidis and Dr. Malli, reviewed the initial draft. VSL: Critical revision of the manuscript for important intellectual content, approval of the paper.

Compliances with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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