ARTICLE

Clinical Research

Liraglutide improves memory in obese patients with prediabetes or early type 2 diabetes: a randomized, controlled study

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Abstract
Background/objectives Diabetic subjects are at increased risk of subtle cognitive impairment since the disease early stages and of dementia later in life. In animal models, glucagon-like peptide-1 receptor agonizts (GLP1-RAs) have been shown to exert neuroprotective effects, expecially in the memory domain. We assessed whether treatment with a GLP1-RA might affect cognitive functions in type 2 diabetic subjects independently on the weight loss it might induce.
Subjects/methods Forty metformin-treated obese subjects with prediabetes or newly diagnosed type 2 diabetes mellitus, received liraglutide (1.8 mg/d) ($n = 20$) or lifestyle counseling (dietary intervention and exercise training) ($n = 20$) until achieving a modest and comparable weight loss (−7% of initial body weight).
Interventions/methods A detailed neuropsychological assessment before and after weight loss was completed in 16 patients per arm, who were administered a total of seven psychological tests, thus assessing three composite domain z-scores for attention, memory, and executive control.
Results After comparable weight loss and superimposable glycemic control and insulin sensitivity, a significant increase in short term memory (mean Digit Span Z score from −0.06 to 0.80, $p = 0.024$) and memory composite z-score (mean memory z-score from −0.67 to 0.032, $p = 0.0065$) was observed in the liraglutide exposed subjects (between group $p = 0.041$ and $p = 0.033$, respectively).
Conclusions Liraglutide might slow down memory function decline in diabetic patients in early, and possibly preclinical stages of the disease.

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Introduction

Type 2 diabetes mellitus is increasingly recognized as a major risk factor for cognitive decline and dementia [1, 2], conferring a relative risk of 2.48 for vascular dementia and of 1.46 for Alzheimer's disease. In addition, both midlife total body obesity and abdominal obesity per se also increase the risk of both Alzheimer's disease and vascular dementia [3, 4].

The pathophysiological mechanisms linking diabetes and cognitive impairment are still unclear, although several large epidemiological studies have suggested that vascular and/or metabolic factors such as hyperglycemia [5, 6] and insulin resistance [7] or by-products of concurrent obesity, such as visceral fat, adipocytokines, nonalcoholic fatty liver disease [8] might be implicated, whereas the contribution of subcutaneous fat to cognitive impairment is less clear, with some reports showing no influence or even a protective effect [9].

Even without dementia, individuals with prediabetes and early type 2 diabetes mellitus frequently display slight cognitive decrements [10] affecting several domains, including verbal memory, attention, and executive functioning. This might lead to concentration difficulties, increased mental effort or forgetfulness. Thus, it is conceivable that mechanisms antecedent overt hyperglycemia, such as insulin resistance or adipose tissue inflammation, may trigger these initial, preclinical cognitive decrements. Consistently, while trials targeting patients with long-standing and poorly controlled diabetes failed to demonstrate a positive effect of intensive glucose control on cognitive impairment [11], it is still possible that these subtle decreases in cognitive abilities may be reversed by precocious interventions targeting adiposity and/or glucose metabolism in the earlier stage.

In the last few years, a novel class of diabetes drugs, glucagon-like peptide-1 receptor analogs (GLP-1-RA) have been introduced for treatment of type 2 diabetes mellitus and obesity [12, 13]. Besides improving glucose control and promoting weight loss, in particular visceral fat loss [14], GLP-1 RA has been shown in animal models to exert neuroprotective effects, probably by influencing the GLP-1 receptors in the central nervous system (CNS) [15–17]. Thus, these molecules could potentially improve cognitive ability both directly, through effects on the CNS, and indirectly, by acting on metabolic pathways eventually influencing cognitive functions. However, to our knowledge, no study has so far explored GLP-1 RAs effects on cognitive ability in individuals with an impairment in glucose metabolism.

Thus, we sought to evaluate, in a group of middle-aged (age range, 49–60) obese subjects with prediabetes or newly-diagnosed type 2 diabetes mellitus, whether treatment by a GLP-1 receptor agonist might affect cognitive functions. To this end, we compared in these subjects changes in psychometric tests scores following liraglutide treatment or a structured lifestyle intervention, after a modest and superimposable weight loss.

Materials/subjects and methods

Study design

This study was part of a longitudinal, randomized, controlled, parallel-arm study designed to assess whether an equal degree of weight loss achieved by liraglutide treatment or lifestyle changes has a different impact on cardiometabolic variables in obese subjects with prediabetes or early type 2 diabetes [14]. In the above-mentioned study, 62 subjects were initially screened and enrolled: the analyses, however, were performed on data from the 40 individuals (20 per arm) who achieved the weight loss target and underwent the post-intervention evaluation. Among the 40 subjects who completed our previous study, neuropsychological assessment before and after weight loss was completed in 32 subjects (16 per arm). Eight subjects, four in each treatment arm, did not repeat the cognitive assessment after achievement of the target weight loss target, because unavailable to undergo the 30–40 min session with the psychologist.

Study protocol and patient characteristics have been previously described in detail [14].

Subjects were enrolled at the Obesity and Diabetes Clinics of Chieti University Hospital. All study visits and procedures took place at the CeSI-Met (Center on Aging Sciences and Translational Medicine) Clinical Research Center, at the University of Chieti. Each patient provided written informed consent to participate and the Protocol was approved by the University of Chieti Ethics Committee.

This study was performed according to Good Clinical Practice regulations (Good Clinical Practice for Trial on Medicinal Product—CPMP/European Commission-July 1990; Decreto Ministeriale 27.4.1992—Ministero della Sanità) and the Declaration of Helsinki (Hong Kong 1989). By signing the protocol consent form, study participants committed themselves to adhere to local legal requirements.

Eligibility criteria

We enrolled subjects with BMI > 30, with a diagnosis of impaired glucose tolerance or impaired fasting glucose (IFG) or type 2 diabetes since >12 months, according to the American Diabetes Association (ADA) Guidelines [18]. At the time of enrollment, all patients were treated by diet therapy plus metformin at the highest tolerated dose (up to 3000 mg/day) (Supplementary information).

Randomization and allocation

After a baseline evaluation, patients were randomized in a 1:1 ratio to receive liraglutide or lifestyle counseling. A computer-generated random allocation sequence was prepared by the trial statistician in blocks of four participants. Based on the order of inclusion in the study, subjects were assigned a consecutive random number, and then allocated to one of the two treatment groups.

Study medication was supplied to the research pharmacy by Novo Nordisk as liraglutide 6.0 mg/mL in 3-mL prefilled pen injectors. Liraglutide treatment was administered by daily subcutaneous injection at bedtime and initiated with 0.6 mg per day (first week), and titrated over a 3-week period to 1.2 mg daily (second week) and to 1.8 mg daily (third week), based on the clinical response and side effects. The non-attainment of the 1.8 mg dose level did not constitute a withdrawal criterion.

Both groups received lifestyle and diabetes education, as part of the standard care. Patients in the liraglutide arm were invited to continue with their usual dietary habits and physical activity.

Outcome and study visits

Participants stayed on the assigned treatment until loosing 7% of their initial body weight (calculated on body weight at baseline visit, at the time of randomization).

Patients not achieving this amount of weight loss within 15 months since randomization discontinued treatment and their data (as well as those of subjects who dropped out from the study or who did not accept to perform the proposed neuropsychological evaluation) were not included in the calculations. After signing the informed consent, subjects were evaluated at baseline and after reaching the pre-specified weight loss. Both visits included: clinical evaluation; abdominal MRI for intrahepatocellular lipid content and adipose tissue quantification with visceral adipose tissue (VAT) and subcutaneous adipose tissue assessment [19]. Moreover, at each visit, blood samples were obtained after a 12-h overnight fast for measurement of the biochemical variables in study. Right after a frequent sampling OGTT was performed for assessment of insulin sensitivity (Matsuda index, HOMA-IR) [20, 21], and beta cell function (OGTT beta index) [22]. These methods have been previously described in detail [14].

While on treatment, patients were seen every 3 weeks at the Clinical Research Center to reinforce motivation to achieve the weight loss goal and to monitor compliance to liraglutide (missed doses counting) or to lifestyle changes (see below). On each occasion, participants underwent physical examination and were carefully monitored for adverse events.

Lifestyle intervention program

Participants were encouraged to achieve the target weight loss within the first 6 months since randomization. Standard lifestyle recommendations were provided in written form and during periodic, 20-to-30-min individual sessions focused on the importance of a healthy lifestyle. Patients met the nutritionists of staff once a week for the first 4 weeks, then once every 2 weeks for the following 20 weeks, finally once a month (until achievement of the weight loss goal). Participants were encouraged to follow the Food Guide Pyramid and the equivalent of a National Cholesterol Education Program Step 1 diet, to reduce their weight (healthy low-calorie, low-fat diet), and to increase their physical activity (moderate intensity, such as brisk walking, for at least 150 min per week, to approximate at least 700 kcal/week expenditure).

Neurocognitive examination

A detailed neuropsychological (NP) assessment was performed through a brief battery of seven standardized NP tests, including Trail-Making Test A (TMT-A), Trail-Making Test B (TMT-B), visual search matrices (VSM), Forward Digit Span (FDS), Rey–Osterrieth complex figure (ROCF) direct coping, ROCF-recall delayed reproduction trial after 10 min, phonemic verbal fluency task (PVF) was administered to participants.

Trail Making Test (part A and B)

Trail Making Test part A is a commonly used measure of attention and information processing speed [23], and already used previously as a measure of attention [24, 25].

The TMTB is a well-known instrument for describing the attentive function but at the same time it evaluates set-switching ability working memory and inhibition control, (i.e., executive functions); thus, it requires the involvement of executive functions, making it a valid measure of this function [23, 26]. Both parts (A and B) of the Trail Making Test consist of 25 circles distributed over a sheet of paper.

The Rey–Osterrieth complex figure test (ROCF)

The ROCF is a neuropsychological test extensively used in clinical practice to investigate visuospatial constructional functions and visuographic memory [27].

Forward digit span

Digit span is the standard test of verbal short-term memory performance that is routinely used in psychological studies, either as a stand-alone test or as part of a number of psychological assessment batteries. Although various other measures of verbal short-term memory capacity exist, the digit span task is the most widely used one in scientific works [28].

Visual search matrices

Attentional matrices tasks are designed to measure selective attention. Participants are required to find and 'cancel' (cross out) a number of targets among distractors.

Verbal Fluency

The Verbal Fluency Test assesses verbal ability and executive control, and was previously used as a measure of executive function [1].

All tests are psychometric instruments validated on the Italian population [29–31]. A standardized z-score was

calculated by subtracting the appropriate normative mean from the raw score and then dividing by the normative standard deviation. For each cognitive domain, a composite z-score was calculated as follows:

    I. Memory domain z-score: standardized FDS + standardized ROCF-recalls;
   II. Attention domain z-score: standardized TMT-A + standardized VSM;
  III. Executive control domain z-score: standardized TMT-B + standardized PVF.

Where necessary, raw test scores were inverted so that higher scores indicated better cognitive performance. The neurocognitive screening was performed for each patient on the same day as the medical and biological examinations (Supplementary information).

Biochemical measurements

Plasma glucose concentration was measured by the glucose oxidase method, serum insulin and C-peptide levels by immunochemiluminometric assays. Serum hs-CRP concentrations were measured using highly sensitive immunoassay. HbA_{1c} levels were determined by automated high-performance liquid chromatography assays standardized to Diabetes Control and Complications Trial values.

Statistical analysis

In the original study, 20 patients were to be studied in each treatment group for a two-tailed alpha of 0.05 and a power of 90% to detect, at the end of the treatment period, a mean difference in the VAT areas of at least one standard deviation (of the distribution of VAT changes) between liraglutide and lifestyle intervention. With 32 (16 per arm) patients undergoing the neuropsychological assessment, the study had a 80% power to detect, at the end of the treatment period, a mean difference in the memory z-score of at least one standard deviation (of the distribution of memory z changes) between liraglutide and lifestyle intervention.

The Kolmogorov–Smirnov test and examination of residual distribution were used to determine whether each variable had a normal distribution. When necessary, natural-log transformation was used to normalize the data, or appropriate nonparametric tests were used (Mann–Whitney U test, Spearman correlation coefficient). Comparisons of baseline data between groups were performed by chi-squared statistics, Fisher exact tests, unpaired Students t tests or Mann–Whitney U tests, as appropriate.

The primary outcome of the intervention study was the change in each of the cognitive functions explored (delta, pre minus post) after achievement of the target weight loss.

For the primary analysis, we used a linear mixed-effects model for repeated measures over time, with delta z-score of each cognitive measurement explored as the dependent variable, study group and time-by-group interaction as fixed effects, time-to-weight loss and baseline z-score of each cognitive measurement as fixed effect covariates and patients and error as random effects. Within the mixed model, we obtained least-squares estimates of the treatment differences and standard errors, and estimated 95% confidence intervals (CIs) and P values for the two prespecified intergroup contrasts (liraglutide and lifestyle intervention) for baseline and end of study within each group. Adjustment for baseline values of cognitive endpoints (for example, baseline DSZ when evaluating change in short-term memory and baseline memory Z-score when evaluating the composite memory endpoint) was also carried out. Within-group and relative effect sizes were calculated using Cohen's ds, using difference from baseline and pooled standard deviation for each time point. Mediation analysis was conducted using PROC CAUSALMED in SAS.

Two-sided P value < 0.05 was considered as statistically significant. Data are expressed as median (interquartile range) unless otherwise specified. The data analysis was generated using SAS/STAT software, Version 9.1.4 of the SAS System for Windows©2009. SAS Institute Inc. and SAS are registered trademarks of SAS Institute Inc., Cary, NC, USA.

Results

Baseline

Table 1 shows the clinical and biochemical characteristics of the 32 patients in the study.

At baseline, both groups showed subtle cognitive decrements for the majority of cognitive domains, except for long-term visuographic memory, which was more compromised, with a performance >1 SD below normal in both groups, and visuospatial sustained attention and cognitive switching ability, which were in the normal range (Table 1). No difference in any cognitive task at baseline was observed between subjects assigned to the two different arms (Table 2).

Intervention study

Median time-to-weight loss (which corresponds by protocol to the duration of the intervention) was 4 months [median (interquartile range) 4 (3–6) months], without any difference between the two arms. During the treatment period, four patients referred nausea and/or abdominal discomfort in the liraglutide arm, although

Table 1 Clinical and laboratory baseline characteristics of obese patients randomized to liraglutide- or lifestyle-induced weight-loss intervention.

Variable	Pre-liraglutide ($n = 16$)	Pre-lifestyle ($n = 16$)	p value*
Age (years)	57 (49–64)	53 (52–58)	0.401
Gender (male), n (%)	9 (56.2)	7 (43.7)	0.724
BMI (kg/m^2)	36.7 (35.3–40.2)	35.0 (31.0–40.1)	0.144
Type 2 diabetes, n (%)	8 (50)	7 (43.7)	–
IGT/IFG, n (%)	8 (50)	9 (56.2)	–
Waist (cm)	119.5 (112.0–128.0)	110.0 (101.7–115.5)	0.014
Systolic BP (mmHg)	147.5 (136.0–154.0)	137 (123–145)	0.065
Diastolic BP (mmHg)	83.0 (78.5–87.0)	80 (70–84)	0.165
Smoke, n (%)	3 (18.7)	0 (0)	0.333
Hypertension, n (%)	14 (87.5)	11 (68.7)	0.394
Dyslipidemia, n (%)	7 (43.7)	9 (56.2)	0.724
CVD, n (%)	1 (6.2)	5 (31.2)	0.171
Previous MI, or revascularization, n (%)	0 (0)	1 (6.25)	–
Previous TIA/stroke, o revascularization, n (%)	1 (6.25)	1 (6.25)	–
PAD, n (%)	1 (6.25)	0 (0)	–
Carotid stenosis, n (%)	0 (0)	3 (18.7)	0.099
Microvascular disease, n (%)	0 (0)	0 (0)	–
Total cholesterol (mg/dL)	178.0 (145.5–193.5)	167.5 (141.0–177.0)	0.209
HDL cholesterol (mmol/L)	47.0 (39.5–52.5)	42 (37–52)	0.464
Triglycerides (mg/dL)	122.5 (86.5–160.5)	90.0 (72.0–119.0)	0.074
Fasting plasma glucose (mg/dL)	92.5 (89.5–103.5)	97 (91.5–102.5)	0.871
HbA1c (%)	5.9 (5.6–6.6)	6.1 (5.7–6.6)	0.890
HbA1c (mmol/mol)	41 (38–49)	43 (40–49)	0.890
Creatinine (mg/dL)	0.70 (0.66–0.86)	0.80 (0.68–0.90)	0.317
Total bilirubin (mg/dL)	0.60 (0.45–0.90)	0.60 (0.45–0.76)	0.569
hs-C-reactive protein (mg/dL)	0.29 (0.18–0.86)	0.29 (0.08–0.48)	0.656
AST (U/L)	33.0 (23.5–39.0)	32 (25–43)	0.626
ALT (U/L)	41.0 (36.5–47.5)	45 (32–62)	0.637
Metformin, n (%)	16 (100)	16 (100)	–
ACE-I, n (%)	4 (25)	3 (18.7)	–
ARBs, n (%)	5 (31.2)	5 (31.2)	–
Diuretics, n (%)			
B-blockers, n (%)	5 (31.2)	4 (25)	–
CCA, n (%)	0 (0)	1 (6.2)	–
Statins, n (%)	2 (12.5)	5 (31.2)	0.394
Fibrates, n (%)	0 (0)	0 (0)	–
PUFA, n (%)	0 (0)	0 (0)	–
Proton pump inhibitors, n (%)	3 (18.7)	3 (18.7)	–
ASA, n (%)	0 (0)	3 (18.7)	0.225

Data are median (25th–75th percentile).

BMI body mass index, *BP* blood pressure, *IGT* impaired glucose tolerance, *IFG* impaired fasting glucose, *WHR* waist–hip ratio, *CVD* cardiovascular disease, *MI* myocardial infarction, *TIA* transient ischemic attack, *PAD* peripheral artery disease, *ACE-I* ACE-inhibitors, *ARBs* angiotensin receptor blockers, *B-block* beta-blockers, *CCA* calcium channel antagonists, *ASA* acetylsalicylic acid.

*Determined by Mann–Whitney or χ^2 test, as appropriate.

symptoms were referred as mild and no drug withdrawal was registered.

Table 2 shows the cognitive performance z-scores and changes in the outcome variables across the two time points of the 32 patients in whom neurocognitive assessment was performed both before and at the end of the study (16 patients randomized to liraglutide and 16 to lifestyle).

Table 2 Neuropsychological performance of obese patients before and after liraglutide- or lifestyle-induced weight loss.

Neurocognitive variable	Pre-lifestyle M (SD)	Post-lifestyle M (SD)	Effect-size (Cohen's d)	P value	Pre-liraglutide M (SD)	Post-liraglutide M (SD)	Effect-size (Cohen's d)	P value	P value (delta between groups)
Neuropsychological test (standardized z score)									
Trail Making A z	0.69(0.43)	0.72 (0.56)	0.06	0.750	0.82 (0.63)	0.76 (0.58)	0.31	0.813	0.700
Trail Making B z	0.41 (1.0)	0.30 (1.1)	0.10	0.450	0.38 (0.7)	0.41 (0.77)	0.04	0.935	0.768
Digit span z	0.39 (1.25)	0.29 (0.89)	0.09	0.745	−0.06 (1.1)	0.80 (1.0)	0.82	0.024	0.041
Visual search matrices z	−0.14 (0.84)	0.36 (0.74)	0.63	0.006	−0.31 (0.75)	−0.20 (0.92)	0.13	0.500	0.111
Rey–Osterrieth complex figure (direct) z	−0.52 (1.30)	−0.56 (1.0)	0.03	0.883	0.20 (0.90)	−0.06 (1.47)	0.21	0.347	0.578
Rey–Osterrieth complex figure (delayed) z	−1.35 (1.13)	−1.20 (1.54)	0.11	0.543	−1.28 (1.18)	−0.73 (1.31)	0.44	0.098	0.307
Phonemic verbal fluency z	−0.21 (1.21)	0.12 (1.28)	0.26	0.124	0.06 (1.22)	−0.04 (1.32)	0.07	0.466	0.087
Domain z score									
Memory z	−0.48 (1.02)	−0.45 (0.82)	0.03	0.901	−0.68 (0.77)	0.032 (0.80)	0.90	0.006	0.032
Attention z	0.28 (0.51)	0.54 (0.47)	0.53	0.036	0.23 (0.49)	0.29 (0.47)	0.12	0.619	0.209
Executive z	0.09 (0.96)	0.20 (1.04)	0.10	0.387	0.21 (0.78)	0.18 (0.88)	0.61	0.845	0.467

M mean, *SD* standard deviation.

At the end of intervention, a significant increase in short-term memory (delta Digit Span Z score, 0.85 ± 0.34, $p = 0.024$; Cohen's effect size = 0.82, Table 2 and Fig. 1a) and in the composite memory domain z-score (delta memory Z score, 0.70 ± 0.22, $p = 0.0065$; Cohen's effect size = 0.87, Table 2 and Fig. 1b) was observed in the liraglutide arm, but not in the lifestyle arm (difference between groups: $p = 0.041$ and $p = 0.033$, respectively, Fig. 1a, b and Table 2). When adjusting for baseline values of the related cognitive domain, the difference between groups in the increase in short-term memory was no longer significant ($p = 0.073$) whereas the difference between groups in the increase in the composite memory z-score remained significant ($p = 0.031$) (Table 2). Mediation analysis did not reveal a mediation effect due to changes in VAT or beta index in explaining the observed increases of Digit Span and composite memory z-scores. VAT or beta index were tested as possible mediators because reduction in VAT and improvement in beta-index were significantly higher in the liraglutide arm than in the lifestyle arm [14].

Interestingly, only in the liraglutide arm, the time-to-weight loss, reflecting the length of drug exposure, was directly related to the improvement in both short-term memory (Rho = 0.72, $p = 0.002$) and memory domain z-score (Rho = 0.54, $p = 0.031$) (Fig. 2).

No other differences were observed for other cognitive fuctions metrics (Table 2).

In the lifestyle arm, but not in the liraglutide arm, there was an improvement in selective attention (between-group Cohen's effect size 0.50, $p = 0.053$) and in the composite attention domain z score (between-group Cohen's effect size 0.41, $p = 0.11$), although not reaching statistical between-group significance (Table 2, Fig. 1c, d).

Discussion

Obesity and type 2 diabetes mellitus are associated with cognitive decline later in life and subtle cognitive decrements early in their natural course. Targeting these early and subtle cognitive changes, characterized by 0.3–0.5 SD units lower performance on cognitive tests, is a major challenge, since these decrements, although not indicating early stages of dementia, may lower the threshold for developing clinical symptoms of dementia later in life [32]. The effect size of cognitive decrements is quite consistent across the stages of glucose metabolism impairment, from impaired glucose tolerance to type 2 diabetes mellitus of longer duration, suggesting that they probably start developing in prediabetic stages and evolve only slowly thereafter, over many years [32]. Findings from longitudinal studies support this concept [33].
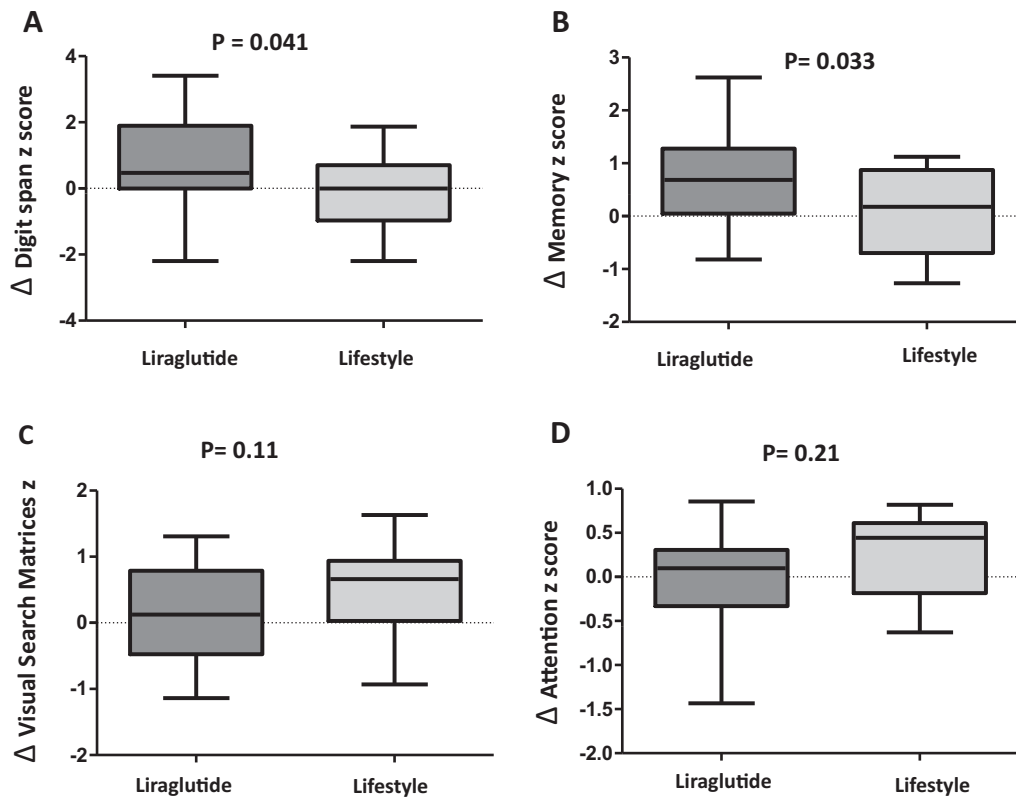
Fig. 1 Effects of liraglutide- or lifestyle-induced weight loss on short-term memory, composite memory domain, selective attention and composite attention domain, in obese subjects with prediabetes or early type 2 diabetes mellitus. Changes in short term memory, as assessed by digit span z score (**a**), and composite memory domain z score (**b**), selective attention, as assessed by visual search matrices z score (**c**), composite attention domain z score (**d**), after liraglutide- or lifestyle counseling-induced weight loss, in obese patients with prediabetes or diabetes diagnosed within one year. P values (lifestyle vs. liraglutide) are for comparison of changes between groups.

Cerebrovascular and neurodegenerative abnormalities observed in the prediabetes phase, prior to the diagnosis of T2DM, contribute to the cerebral complications of T2DM and prediabetes, such as stroke, dementia, and depression [34].

In the present study, we demonstrated that, for the same degree of weight loss, treatment with a GLP-1 RA is more effective than a standardized lifestyle intervention protocol in improving memory performance in a well-characterized group of obese patients with prediabetes or early type 2 diabetes mellitus. To our knowledge, this is the first clinical study assessing the effects of liraglutide on cognitive function performed in the settings of diabetes and obesity. Until now, there has been no good evidence that any specific treatment or treatment strategy for type 2 diabetes can prevent or delay cognitive impairment, due to paucity of clinical trials, with an high risk of performance and detection bias, small sample sizes, and imprecise estimates of the effects [35]. The only small trial, performed on 39 elderly subjects with type 2 diabetes, did not show any measurable effect on cognitive function with any incretin-based therapy (18 patients, on DPP-4 or

liraglutide) or with a sGLT2-inhibitor administered for 12 months [36].

Among strategies approved for the treatment of obesity and diabetes, liraglutide has emerged as a potentially valuable candidate, beyond its positive effects on body weight and glycemic control, in light of the neuroprotective properties exerted in preclinical studies, especially in the memory domain [16, 17]. Indeed, GLP-1Rs have been found in the neuronal cell body and dendrites in the central nervous system, in particular in the hypothalamus, hippocampus, cerebral cortex, and olfactory bulb [37]. Liraglutide and the other synthetic GLP-1RAs are able to readily cross the blood brain barrier, reaching the brain almost intact and thereby exerting neuroprotective effects [38]. In animal models, both liraglutide and exenatide have been shown to exert their effects by reducing oxidative stress and enhancing antioxidant capacity, decreasing inflammation and apoptosis, reducing amyloid plaque volume, preventing synaptic loss, improving neuronal plasticity, and promoting neurogenesis by acting on progenitor cells [39, 40]. In experimental models, incretins delay cognitive decline, improve learning and memory performance and reduce the
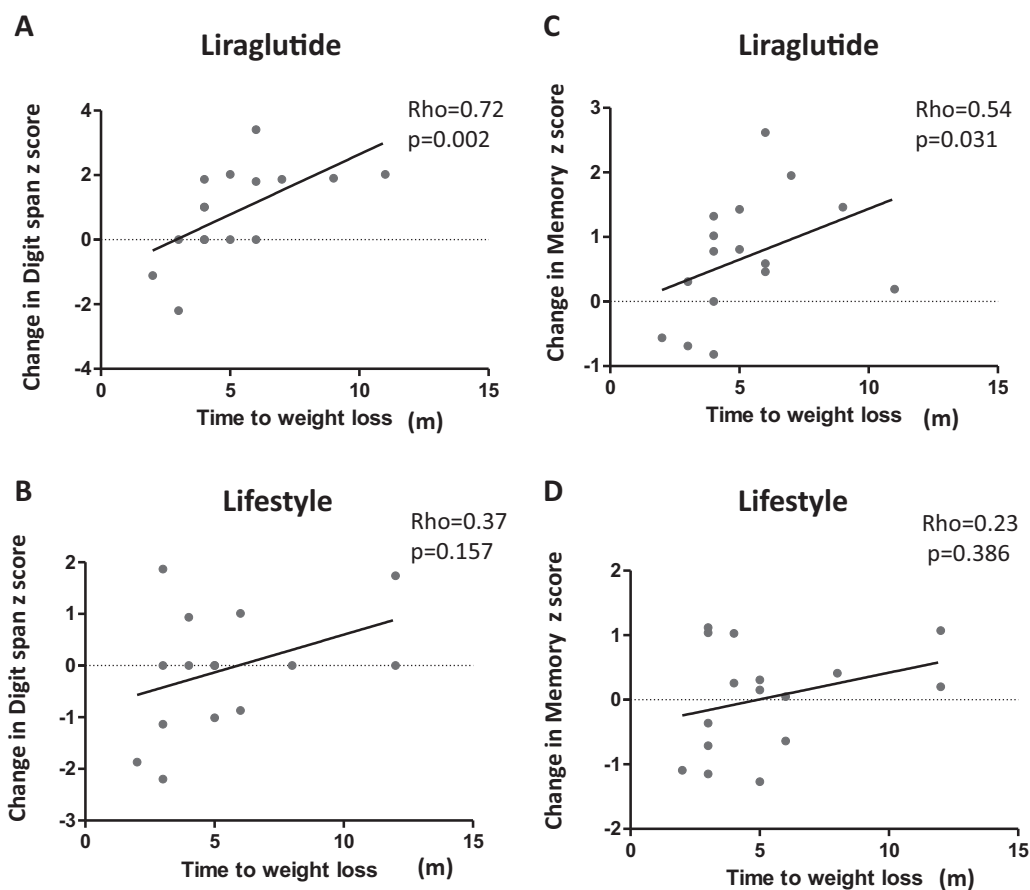
Fig. 2 Correlation between time-to-weight-loss and change in short term memory or in the composite memory-domain throughout the treatment period in the liraglutide and lifestyle arms. Correlation between time to weight loss and change in short term memory, as assessed by digit span *z* score, in Liraglutide (**a**), and in Lifestyle arms (**c**), and correlation between time to weight loss and change in the composite memory domain *z*-score in the liraglutide (**b**) and lifestyle arms (**d**) in obese patients with prediabetes or type 2 diabetes diagnosed within one year.

burden of amyloid toxicity in mouse models of Alzheimer's disease [15, 17]. Ongoing human trials reported or anticipate a neuroprotective effect of GLP-1-RAs in Parkinson's and Alzheimer's disease [41, 42]. In patients with mood disorders, liraglutide has recently been associated with improvements in objective measures of cognitive dysfunction, an effect attributed to concurrent weight loss [43]. In fact, weight loss appears to be associated with low-order improvements in cognitive functions in obese individuals, although with controversial findings [44, 45]. Indeed, long-term weight loss intervention in obese patients with type 2 diabetes mellitus randomized to intensive lifestyle intervention may reduce the adverse impact of diabetes on brain structure, but does not reduce the risk of cognitive impairment [46].

The design of our study, involving a control group of subjects randomized to a lifestyle intervention until achieving the same degree of weight loss, allowed discrimination between a direct effect of the drug and a positive effect mediated by the weight loss achieved with liraglutide.

In comparison with lifestyle changes, liraglutide-related weight loss was associated with significantly higher Cohen's effect sizes of 0.71 (from 0.09 to 0.80) and 0.83 (from 0.03 to 0.90) on working memory and composite memory, respectively. This translates into a 70–80% (relative to one standard deviation) improvement in the memory performance. Of note, the extent of the effect on the cognitive performance is higher than that achieved by a computerized cognitive training program [47]. Interestingly, the magnitude of the effect on memory ability was linearly and directly related to the treatment duration only in the liraglutide arm, suggesting that the length of drug exposure, instead of the extent of weight loss, is the main determinant of the outcome. Thus, it is conceivable that the longer the treatment duration, the more significant the effect of liraglutide on memory performance.

Vice versa, in our study, lifestyle intervention-related weight loss was associated with improvement in selective attention and in the composite attention domain *z*-score, in keeping with previous observations.

Limitations of the study include the small sample size and the relatively short median duration of the study (3–12 months), based on the time to achievement of the weight loss target. Serial testing over a relatively short period of time may be associated with improvements in test performance attributed to increasing familiarity with and exposure to test instruments, a phenomenon known as practice effect. We cannot exclude that a practice effect might have interfered with the results, although the comparable median time-to-weight loss in the two arms is likely to have mitigated such effect. Moreover, a practice effect is not supported by the linear correlation between the length of liraglutide exposure and the improvement in the composite memory z-score. On the contrary, we can hypothesize that liraglutide intervention would be more likely to be effective if applied over a long period. Finally, no brain imaging has been performed in addition to neurocognitive tests.

Prediabetic and diabetic patients are characterized by a greater risk of developing some degree of cognitive impairment. Thus, preventing and controlling diabetes onset might prove beneficial in reducing future cognitive decline. Liraglutide is able to prevent and/or reverse memory function, thus confirming the neuroprotective effects observed in experimental models, whereas life-style intervention seems to ameliorate attentive functions. Therefore, it is plausible that a therapeutic approach involving diet, physical activity and incretin analogs in patients with diabetes since the preclinical stages might be beneficial against cognitive deficits. Large-scale clinical trials are warranted.

Author contributions FV, PGS, and FS contributed to the study design and protocol, the analysis plan, the supervision of the analysis, study implementation, data acquisition and interpretation, statistical analyses, writing of the manuscript, and critical revision and final approval of the manuscript. PGS and AB contributed to study implementation, data acquisition and interpretation, and writing of the manuscript. MTG, FC, RL, and RT contributed to study implementation, data acquisition and interpretation, and final approval of the manuscript. ADC contributed to statistical analysis and data interpretation. AC contributed to the supervision of the analysis, data interpretation, writing of the manuscript, and critical revision and final approval of the manuscript. FS, FV, and AC are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with ethical standards

Conflict of interest AC received lecture fees and fees for serving on advisory boards from Novo Nordisk, Eli Lilly, AstraZeneca, Sanofi Aventis, Merck Sharp & Dohme, and Takeda; and grant support to his institution from Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

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