Cognitive Outcomes In Adults Treated With GLP-1 Receptor Agonists Compared To Non-Users: A Retrospective Chart Review

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Introduction

Insulin resistance and type 2 diabetes mellitus (T2DM) are associated with an increased risk of cognitive decline [1]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) improve glycemic control in patients with T2DM and reduce body weight in a broader population. Emerging evidence suggests that GLP-1 RAs may also exert neuroprotective effects by reducing neuroinflammation and enhancing neuroplasticity, potentially lowering the risk of dementia or preserving cognitive function [2, 3]. While prospective studies are needed to establish causal relationships, real-world evidence can provide insights into underlying mechanisms of action and help characterize treatment response variability in historically underrepresented or understudied populations.

Objective

To evaluate the association between GLP-1 receptor agonist therapy and changes in cognitive function, as measured by the Mini-Mental State Examination (MMSE), in adults receiving routine clinical care.

Methods

This retrospective cohort study used de-identified electronic medical records (EMRs) from Gonzaba Medical Group. Adults aged 18 years or older with at least two MMSE assessments and complete data for relevant clinical and demographic variables were included (n = 529).

Participants were grouped based on GLP-1 RA use. Baseline characteristics included age, sex, body mass index (BMI), diabetes status, and MMSE score.

Linear regression models were used to evaluate the association between GLP-1 RA exposure and changes in MMSE and BMI over time, adjusting for available covariates.

This study was submitted to Advarra Institutional Review Board, which formally determined that it met criteria for exemption from IRB oversight under applicable federal regulations [4].

Results

A total of 529 individuals met inclusion criteria, including 78 who received GLP-1 RA therapy and 451 non-treated controls. Demographic and baseline characteristics are summarized in Table 1.

Table 1. Demographics and Baseline Characteristics (Unadjusted)

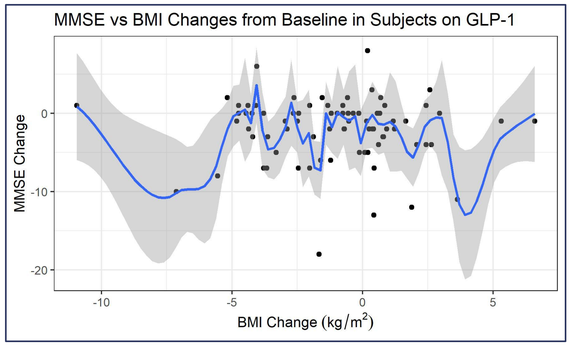
Characteristic	GLP-1 (N=78)	Control (N=451)	P-value
Sex			
Female	62.82% (49)	56.10% (253)	0.2680
Male	37.18% (29)	43.90% (198)	
Ethnicity			
Hispanic or Latino	93.59% (73)	96.90% (437)	0.1474
Not Hispanic or Latino	6.41% (5)	3.10% (14)	
Age (Years)	70.6 (4.81)	75.0 (6.99)	<0.0001
BMI Baseline (kg/m^2)	33.9 (6.59)	29.0 (5.39)	<0.0001
Diabetes			
Yes	84.62% (66)	47.89% (216)	<0.0001
No	15.38% (12)	52.11% (235)	
MMSE Baseline	27.2 (3.32)	25.0 (4.41)	<0.0001
Time between MMSE (Years)	3.2 (1.41)	2.1 (1.46)	<0.0001

Percentage (Count) with Chisq test for categorical variables
Mean (Standard Deviation) with T-test for continuous variables

Statistically significant differences between groups at baseline were observed in age, baseline BMI, diabetes prevalence, baseline MMSE scores, and the time interval between MMSE assessments. Compared to controls, GLP-1 RA-treated participants were younger, had a higher mean BMI, were more likely to have a diagnosis of type 2 diabetes, and had higher baseline MMSE scores. The cohort was predominantly Hispanic, reflecting the source population.

GLP-1 RA–treated participants experienced a significantly greater reduction in BMI compared to controls (-0.91 kg/m², $p < 0.01$). Cognitive decline occurred in all groups. Though not statistically significant ($p = 0.69$), in the GLP-1 RA–treated group, each 1 kg/m² reduction in BMI was associated with a 0.067-point relatively higher MMSE score at follow-up.

Figure 1: Locally Estimated Scatterplot Smoothing (LOESS) Regression Plot



The LOESS plot (Figure 1) provides a non-parametric visualization of the relationship between change in BMI and change in MMSE score from baseline to follow-up among GLP-1 RA–treated participants. Data from untreated participants were not included in the smoothing model.

Discussion

This retrospective cohort study offers preliminary evidence that GLP-1 receptor agonist (GLP-1 RA) treatment may be associated with patterns suggestive of cognitive preservation in real-world populations. Although a statistically significant association between weight reduction and cognitive outcomes was not observed, the direction of the findings aligns with emerging hypotheses regarding the neuroprotective potential of GLP-1 RAs.

These results contribute to the growing body of literature examining the intersection of metabolic health and cognition, and they highlight the utility of real-world data for assessing treatment effects across more diverse and clinically representative populations. The observed relationship between BMI reduction and follow-up cognitive status within the GLP-1 RA treated group, while not statistically significant, may merit further exploration in adequately powered prospective studies.

Several limitations should be acknowledged. Baseline imbalances in age, sex, and comorbidities between treatment groups may confound the interpretation of observed associations. In addition, the LOESS curve was generated using data from the treated group only, which limits the ability to make direct comparisons with the control cohort. Nonetheless, these exploratory analyses may help inform future investigations of potential mechanistic links, whether mediated through central nervous system pathways or influenced by peripheral metabolic improvements, between GLP-1 RA therapy and cognitive trajectories.

Conclusion

In this exploratory analysis, greater reductions in BMI among GLP-1 RA–treated participants were associated with relatively higher MMSE scores at follow-up, although the association was not statistically significant. These findings may support further investigation into the potential role of metabolic improvements in cognitive outcomes and highlight the importance of prospective studies to clarify underlying mechanisms.

References

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