Are the Neurocognitive Effects Attributed to Incretin Therapy Centrally or Peripherally Regulated?

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INTRODUCTION

- Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are established for their metabolic and glycemic benefits and have been associated with neurocognitive improvements. [1,2]
- GLP-1 RAs direct central nervous system activity includes hypothalamus and brain stem regulation of stress and mood. GLP-1 RAs peripheral metabolic changes linked to cognitive function includes improved glycemic control, weight loss, or reduced inflammation. [3]
- Both central and peripheral effects are possible drivers of the GLP-1 RA-associated neurocognitive improvements, but the dominant mechanism remains debated.
- Understanding pathways is important for the design and tolerability of future incretin-based therapies.

OBJECTIVE

To evaluate the relationship between weight loss and cognitive function among adults treated with GLP-1 receptor agonists to clarify whether neurocognitive benefits arise primarily from peripheral metabolic improvements or direct central nervous system effects.

METHODS

This retrospective cohort analysis evaluated adults treated with GLP-1 RAs in a predominantly Hispanic, urban population, identified from de-identified electronic medical records (EMRs) from Gonzaba Medical Group (n=78).

Inclusion required at least two Mini-Mental State Examination (MMSE) scores and available BMI data.

Linear regression was used to assess the association between change in BMI and change in MMSE score, adjusting for demographic and clinical 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].

Table 1. Demographic Characteristics

Total	N=78
Sex	
Female	49 (62.82%)
Male	29 (37.18%)
Ethnicity	
Hispanic or Latino	73 (93.59%)
Not Hispanic or Latino	5 (6.41%)
Age at Baseline (years)	70.6

Abbreviations: T2D, Type 2 Diabetes; MMSE, Mini-Mental State Examination; BMI, Body Mass Index

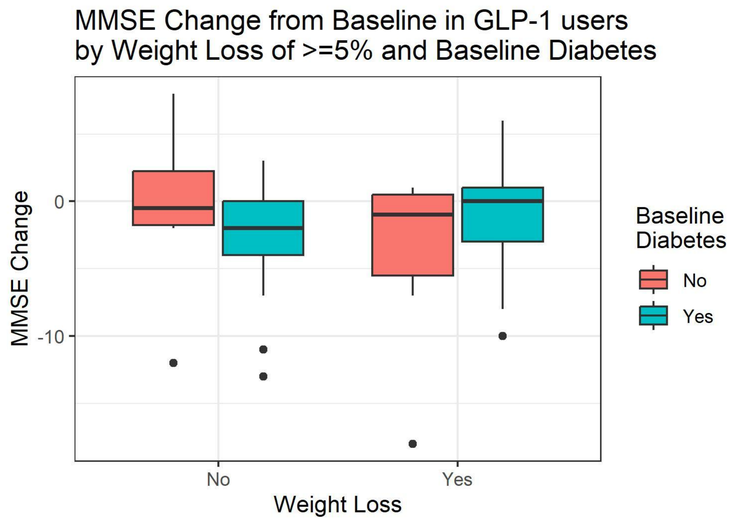
Baseline BMI
33.9 kg/m^2

Baseline T2D Diagnosis
Yes: 84.62% (66)
No: 15.38% (12)

Baseline MMSE
27.2

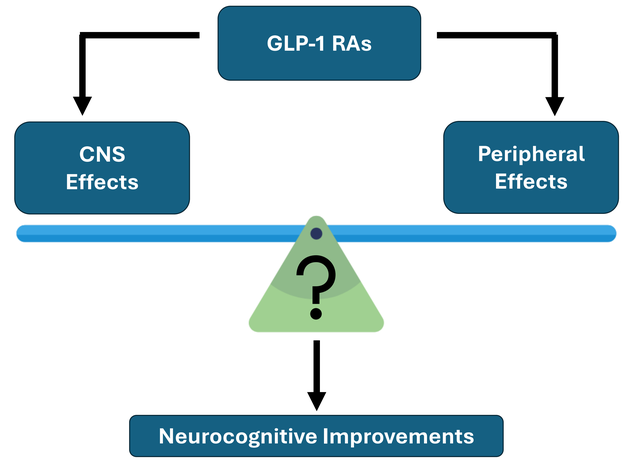
Time between MMSE
3.2 years

RESULTS



GLP-1 RA–treated participants experienced a significant mean reduction in BMI (–0.91 kg/m², $p < 0.01$). Each 1 kg/m² decrease in BMI was associated with a 0.067-point higher MMSE score at follow-up, although this association did not reach statistical significance ($p = 0.69$). This finding is directionally consistent with the hypothesis that metabolic improvements may help preserve cognitive function in this population. Recent large-scale analyses have also found that GLP-1 RA or semaglutide use is associated with a substantially lower likelihood of receiving a dementia diagnosis compared to other antidiabetic medications, even after accounting for weight and glycemic changes.

Hypothesis Generating



CONCLUSION

Greater weight loss on GLP-1 RAs was associated with a trend toward cognitive preservation. These exploratory findings suggest that metabolic improvements may contribute to neurocognitive benefit and support further investigation into the relative roles of peripheral and central mechanisms in incretin therapy..

REFERENCES

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