Eustachian Tube Disorders in Patients Prescribed Glucagon-like Peptide 1 Agonists: A Propensity Score Matching Analysis

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Introduction

- Glucagon-like Peptide-1 (GLP-1) receptor agonists (RAs) are used to treat Type 2 diabetes mellitus (T2DM) and obesity
- GLP-1 RAs stimulate GLP-1 receptors -> decrease gastric motility, increase insulin sensitivity -> weight loss, improved glycemic control, and decrease risk of cardiovascular disease
- 40% of US adults affected by obesity and 11.6% by diabetes
- Potential impact of GLP-1 RA on eustachian tube volume may result in Eustachian tube dysfunction (ETD) though limited reports in published literature
- Rapid weight loss may reduce the volume of Ostmann fat pad surrounding the eustachian tube predisposing to patulous eustachian tube
  - Seen in 10.5-47.3% of patients after bariatric surgery

GLP-1 RA Medication	Mechanism	For T2DM	For Weight Management
Semaglutide	Long acting GLP-1 RA	✓	✓
Dulaglutide	Long-acting GLP-1 RA	✓	
Liraglutide	Short-acting GLP-1 RA	✓	✓
Exenatide	Short and long-acting GLP-1 RA	✓	
Tirzepatide	Dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) RA	✓	✓

Aim

To examine the association between GLP-1 RA use and the development of eustachian tube dysfunction, including patulous eustachian tube and obstructive eustachian tube dysfunction, in patients with T2DM or obesity using a large, multi-institutional cohort

Methods and Materials

Study Design
Retrospective cohort study utilizing TriNetX: a globally federated research network with deidentified electronic medical records. Utilized the Global Collaborative Network containing data from 135 healthcare organizations and over 150 million patients.

Cohorts
- Two cohorts (18 years and older):
  1) **GLP-1 RA**: Diagnosis of **T2DM** and at least one recorded prescription for GLP-1 following diagnosis
  2) **No GLP-1 RA**: Diagnosis of **T2DM** with no recorded prescription for GLP-1 at any time
- Subgroup analyses evaluated each individual GLP-1 RA medication
- Secondary analysis included obese/overweight adults without diabetes to assess GLP-1 RA use for weight loss

Outcomes
- Primary outcome: Eustachian tube dysfunction (ETD)
- Secondary outcomes: Patulous eustachian tube (PET), Obstructive Eustachian tube dysfunction (OETD)

Analysis
- Index event was T2DM (or obese/overweight diagnosis for non-diabetic cohort) with GLP-1 RA use if applicable.
- Patients with prior ETD or index >20 years before were excluded.
- Propensity score matching was performed on age, sex, race, ethnicity, and comorbidities. Balance was assessed by SMD <0.1.
- Odds ratios were calculated; p<0.05 was significant.

Results

Table 1. Demographics of GLP-1 and No GLP-1 Cohorts **Before** Matching

Variable	GLP-1 Cohort, No. (%)	No GLP-1 Cohort, No. (%)
Patients, No.	825,439	6,467,930
Age (SD)	61.1 (13.1)	69.4 (14.7)
Gender (Female)	460,470 (55.8%)	3,043,772 (49.1%)
White Race	537,450 (65.1%)	3,395,280 (54.8%)
Black Race	147,394 (17.9%)	974,542 (15.7%)
Hypertension	561,819 (68.1%)	1,329,740 (21.5%)
Overweight/obese	415,154 (50.3%)	537,440 (8.7%)

Table 2. Demographics of GLP-1 and No GLP-1 Cohorts **After** Matching

Variable	GLP-1 Cohort, No. (%)	No GLP-1 Cohort, No. (%)
Patients, No.	712,113	712,113
Age (SD)	62.0 (13.0)	61.3 (14.3)
Gender (Female)	389,453 (54.7%)	388,410 (54.5%)
White Race	454,869 (63.9%)	462,417 (64.9%)
Black Race	127,083 (17.8%)	126,802 (17.8%)
Hypertension	450,321 (63.2%)	460,219 (64.6%)
Overweight/obese	303,340 (42.6%)	311,754 (43.8%)

Cohorts matched across all variables with SMD <0.1 after matching

Primary Analysis of T2DM patients (Figure 1):

Follow-up: Mean (SD) 3.07 (2.75) years
ETD incidence: 1.32% (GLP-1) vs 1.03% (No GLP-1)
GLP-1 use → ↑ **odds of ETD** (OR 1.28, 95% CI: 1.24–1.32)

PET incidence: 0.014% (GLP-1) vs. 0.010% (No GLP-1)
GLP-1 use → ↑ **odds of PET** (OR 1.39, 95% CI: 1.02–1.88)

OETD: No significant difference between groups

Subgroup: All GLP-1s ↑ odds of ETD
Semaglutide ↑ odds of PET (OR 1.69, 95% CI: 1.07–2.67)

Obesity-only Secondary Analysis (Figure 2):

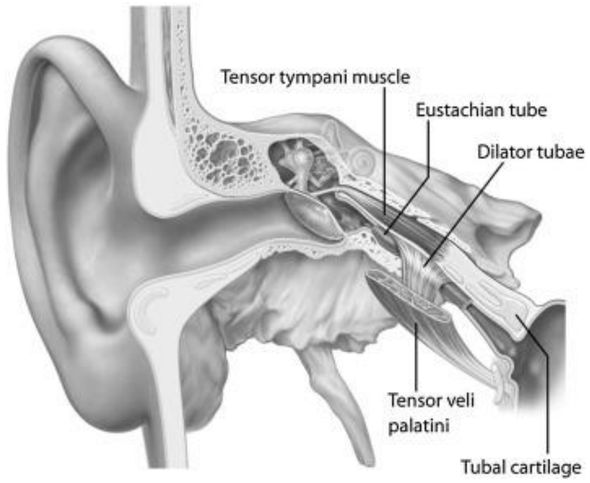
Follow-up: Mean (SD) 1.72 (1.55) years
ETD incidence: 1.42% (GLP-1) vs 1.01% (No GLP-1)
GLP-1 use → ↑ odds of ETD (OR 1.41), PET (OR 2.96) and OETD (OR 1.93)

Discussion

GLP-1 RA use in T2DM patients → ↑ odds of ETD and PET
GLP-1 RA use in obese/overweight → ↑ odds of ETD, PET, and OETD
Different GLP-1 RA medications have varying impacts

Suggested mechanism:
Weight loss → reduced Ostmann fat pad volume → impaired eustachian tube closure → patulous eustachian tube

- Similar associations seen after bariatric surgery with significant weight loss (ETD reported in up to 47% of patients)
- GLP-1s may be associated with OETD because they can worsen gastroesophageal reflux due to slowed gastric emptying
- Diagnoses of ETD, PET and OETD are challenging due to overlapping symptoms, no standardized diagnostic criteria and diagnoses by primary care physicians who often lack access to tympanometry
- Association between GLP-1 use and ETD suggests that the medication has impacts on the function of the eustachian tube



Ostmann fat pads located inferolateral to the cartilaginous eustachian tube can impact the volume of the tube

Figure 1. Forest Plot Demonstrating Odds Ratios of Eustachian Tube Dysfunction, Including Patulous and Obstructive Subtypes, Among **T2DM Patients** Treated vs. Not Treated with GLP-1 Receptor Agonists

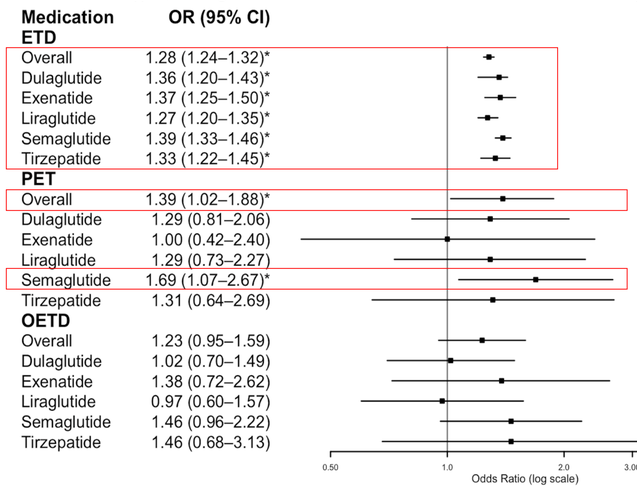
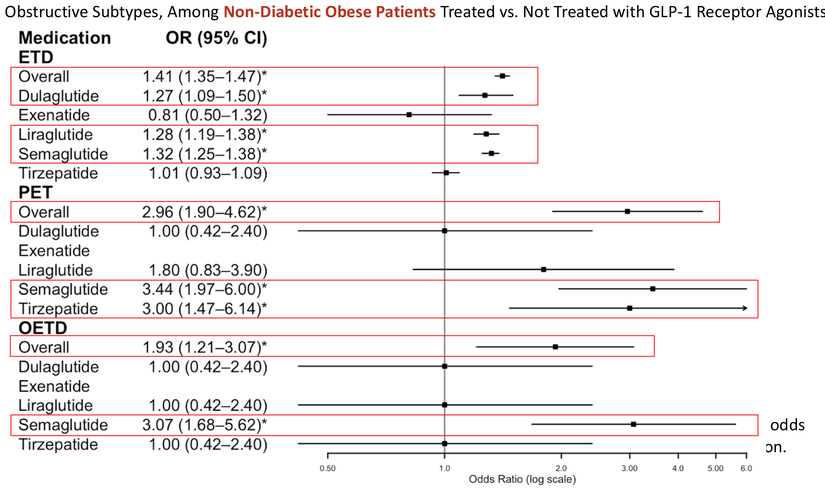


Figure 2. Forest Plot Demonstrating Odds Ratios of Eustachian Tube Dysfunction, Including Patulous and Obstructive Subtypes, Among **Non-Diabetic Obese Patients** Treated vs. Not Treated with GLP-1 Receptor Agonists



Note: ETD = Eustachian Tube Dysfunction, PET = Patulous Eustachian Tube, OETD = Obstructive ETD. OR = odds ratios. OR (95% CI) are displayed on a logarithmic scale. Asterisks indicate statistically significant association.

Conclusion

Prescribers should counsel patients on GLP-1 RA on otologic symptoms, especially during rapid weight loss. Future prospective studies can include weight loss data and standardized definitions of ETD, PET and OETD.

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