Association of GLP-1 Receptor Agonists with Thyroid Dysfunction in Patients with Type 2 Diabetes Mellitus: A Retrospective Cohort Study

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Background

Patients with Type 2 Diabetes Mellitus (T2DM) are prone to thyroid dysfunction (TD). Whether GLP-1 receptor agonists (GLP-1RAs) increase TD risks (hyperthyroidism and hypothyroidism) remains controversial; real-world evidence comparing against adequate active comparators is limited.

Objective

To evaluate the risk of TDs associated with GLP-1RAs compared to SGLT2 inhibitors (SGLT2i) and DPP4 inhibitors (DPP4i) among patients with T2DM.

Methods

This retrospective cohort study used MarketScan® Commercial claims database (2016 - 2024). We included T2DM adults initiating GLP-1RA, SGLT2i, or DPP4i, excluding those with preexisting TDs or prior use of thyroid-affecting therapies. The primary outcome was composite TD, secondary outcomes were incident hypothyroidism and hyperthyroidism. We applied an induction period of 90 days, and follow-up started until outcome, treatment switch/discontinuation, thyroid test discontinuation (240-day grace period), or disenrollment. Propensity score (PS) were estimated via logistic regression based on expert-informed covariates (comorbidities, comedications, diabetes severity score) and 1:1 matching was performed to achieve covariate balance. The Delta method estimated relative risks (RR) and risk differences (RD, per 100) at 90, 180, and 365 days. Subgroup analyses included age, sex, obesity, and baseline insulin use.

Results

After PS matching, the analytic cohorts included 75,833 GLP-1RA vs. SGLT2i patients, and 44,423 GLP-1RA vs. DPP4i patients (standardized mean differences ≤ 0.1). Compared to SGLT2i, increased risk of composite TD was observed at 90, 180, and 365 days (365-day RR 1.14, 95% confidence interval (CI) [1.01, 1.28]; RD 3.13% [0.21, 6.04]). This was driven by incident hypothyroidism (365-day RR 1.22 [1.07, 1.38]; RD 4.42% [1.56, 7.28]). Compared to DPP-4i, GLP-1RAs showed an increased risk of composite TD and hypothyroidism at 90 and 180 days, but were non-significant at 365 days (composite TD RR 0.95 [0.83, 1.10]; hypothyroidism RR 0.99 [0.85, 1.14]). Hyperthyroidism risk was not increased. Subgroup analyses showed increased 90-day TD risk for women, patients ≥ 40 years, and those with obesity across both comparisons. Men and baseline insulin users had increased risk only versus SGLT2i.

Conclusion

GLP-1RAs were associated with increased risk of incident hypothyroidism versus SGLT2i, and an early risk increased compared to DPP4i. Hyperthyroidism risk was not elevated. Routine thyroid function monitoring is suggested for patients initiating GLP-1RAs.

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