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Glucagon-like Peptide-1 Receptor Agonists and Thyroid Cancer: Myth or Reality?

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Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are being used increasingly for the management of type 2 diabetes mellitus (T2DM) or obesity because of their association with robust glucose lowering, weight loss, and cardiorenal benefits.[1] The association between GLP-1RA treatments and thyroid cancer has been a topic of discussion since their early development with the understanding that GLP-1 receptors are present on rodent thyroid parafollicular cells (C-cells), and that GLP-1RAs can cause an increase in calcitonin, and both C-cell hyperplasia and medullary thyroid carcinoma (MTC).[2] This data from rodent studies has led to GLP-1RAs being contraindicated in patients with a personal or family history of MTC or with multiple endocrine neoplasia syndrome type 2.[1]

Despite this contraindication, the human relevance of GLP-1RA induced MTC in rodents has not been proven. Normal or hyperplastic C-cells in humans may not express the GLP-1 receptor, and studies of human MTCs have shown variable expression of the GLP-1 receptor.[3,4] Studies have shown conflicting evidence regarding the expression of the GLP-1 receptor in human papillary thyroid cancer (PTC) cell lines: however, GLP-1RAs did not have significant effects on the proliferation of PTC cells.[4,5]

Because of the data that potentially links GLP-1RAs to an increased risk of thyroid cancer, clinical studies in humans are important in addressing this issue. I will review the relevant data from human studies that have analyzed

the potential link between GLP-1RA treatment and thyroid cancer, including pharmacovigilance and observational studies as well as randomized controlled trials (RCTs).

Pharmacovigilance Studies

Pharmacovigilance databases can be used to analyze spontaneous reports of adverse events in drug treated individuals. Such studies have been conducted for reports of thyroid cancer possibly related to GLP-1RAs. An analysis of the European pharmacovigilance database (EudraVigilance) reviewed all reports of thyroid cancer with GLP-1RAs from their initial marketing through to January 2020. Disproportionality was observed for GLP-1RAs and thyroid cancer as well as MTC, with proportional reporting ratios (PRRs) of 14.4 (95% confidence interval [CI] 11.8–17.4) and 221.5 (95% CI 155.7-315.1), respectively.[6] The Food and Drug Administration Adverse Event Reporting System (FAERS) data from 2004 to 2021 were used for a disproportionality analysis to assess the relationship between GLP-1RAs and all types of neoplasms. This analysis revealed a significant PRR ($p<0.001$) between GLP-1RA and thyroid cancer (PRR 6.89), MTC (PRR 27.43), and PTC (PRR 8.68).[7] Finally, an analysis of the World Health Organization's pharmacovigilance database (VigiBAse) showed signals of disproportionality with GLP-1RA for thyroid cancer (PRR 30.5, 95% CI 25.1–37.2) and for MTC (PRR 28.7, 95% CI 16.1–51.1).[8]

Although pharmacovigilance studies suggest disproportionality with GLP-1RAs and thyroid cancer, these analyses cannot be used to prove causality. Furthermore, selection bias may relate to increased reporting of thyroid cancer in GLP-1RA treated individuals due to the known potential relationship between GLP-1RAs and thyroid cancer (notoriety bias). Detection bias is also likely due to greater surveillance for thyroid cancer in GLP-1RA treated individuals or perhaps weight loss related to GLP-1RA treatment makes thyroid nodules more apparent.

Observational Studies

Figure 1 summarizes the main results of 8 observational studies that have explored the link between GLP-1RAs and thyroid cancer. Using commercial health insurance claims data in the USA (Normative Health Information), Dore et al. reported the results of a retrospective cohort study with propensity matching comparing initiators of exenatide to initiators of metformin or glyburide between 2005 and 2009 with up to 1 year of follow-up. The incidence of thyroid cancer was 37/32,822 (0.1%) amongst the exenatide group and 26/32,842 (0.1%) in the metformin/glyburide group (relative risk [RR] 1.4, 95% CI 0.8–2.4).[9] In another retrospective cohort study using 2 administrative databases in the USA, the median follow-up was 1 year. This study compared 33,629 users of exenatide to 49,317 propensity-score matched users of other antidiabetic drugs (OADs). The incidence rates of thyroid cancer were 0.62 events and 0.44 events per 1,000 patient-years in the exenatide and OAD groups, respectively (hazard ratio [HR] 1.46, 95% CI 0.98–2.19). Results of a time-dependent analysis by duration of treatment or cumulative dose were similar.[10] In 2021, Funch et al. reported findings from a prospective cohort study using data drawn from a US health plan (Optum), comparing propensity score matched initiators of liraglutide versus OADs. Amongst 34,707 individuals treated with liraglutide or OADs (excluding exenatide), who were followed for a median of 1.4 years, the incidence of thyroid cancer was significantly increased in the liraglutide group, with 41 cases compared to 24 cases amongst OAD users (RR 1.70, 95% CI 1.03–2.81).[11] Wang et al. performed a retrospective analysis of a large electronic heath database in the USA (Explorys) and compared 64,230 users of GLP-1RAs to 619,340 users of metformin. Within 5 years of starting medication, GLP-1RA was associated with a significantly higher incident risk of thyroid cancer (adjusted odds ratio [OR] 1.65, 95% CI 1.31–2.05).[12] A nested case-control study by Bezin et al. used the French national health care insurance system database and compared 2,562 individuals with T2DM and thyroid cancer to 45,184 control subjects with T2DM. Current use of GLP-1RA was 8.1% in case subjects and 6.0% in control subjects (HR 1.46, 95% CI 1.23–1.74). Similarly significant results were shown for MTC (15.5% of all thyroid cancer cases), with current GLP-1RA use of 8.8% in case subjects and 5.9% in control subjects (HR 1.76, 95% CI 1.16–2.69). In a cumulative exposure model, use of GLP-1RA for 1–3 years or >3 years was associated with an increased risk of thyroid cancer and use of GLP-1RA for 1–3 years was associated with an increased risk of MTC.[8] A population-based cohort study using claims data from the *Korean National Health Insurance Database*

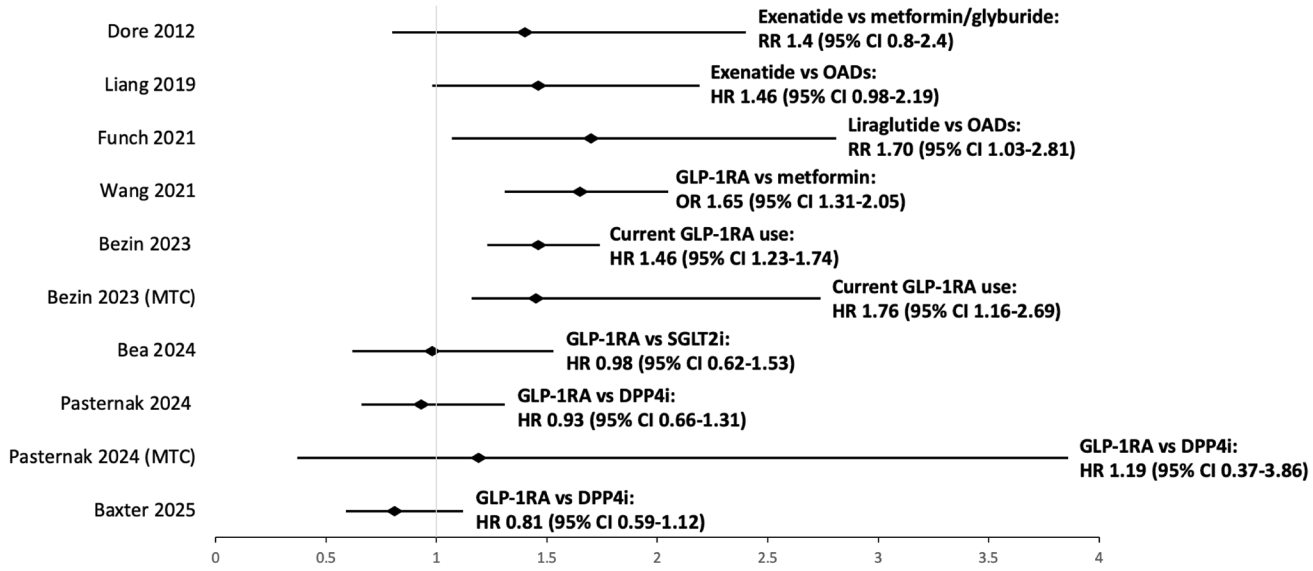

Figure 1. Summary of primary results from observational studies of GLP-1RAs and thyroid cancer; *courtesy of Ronald M. Goldenberg, MD, FRCPC, FACE*.

Except for the Bezin study, data shown for each study compares thyroid cancer risk (or MTC risk where indicated) with GLP-1RA treatment vs comparator. The Bezin study data compares current GLP-1RA use in thyroid cancer cases (or MTC where indicated) to control cases.

Abbreviations: GLP-1RA: glucagon-like peptide-1 receptor agonist, **MTC:** medullary thyroid carcinoma, **RR:** relative risk, **HR:** hazard ratio; **OR:** odds ratio, **CI:** confidence interval, **OADs:** other antidiabetic drugs, **SGLT2i:** sodium-glucose cotransporter-2 inhibitors, **DPP4i:** dipeptidyl peptidase 4 inhibitors.

compared 18,863 new users of GLP-1RAs to 325,307 new users of sodium-glucose cotransporter-2 inhibitors (SGLT2i) after propensity score weighting. The hazard ratio for thyroid cancer for GLP-1RAs vs SGLT2is was 0.98 (95% CI 0.62-1.53).[13] Pasternak et al. investigated the association of GLP-1RAs with an increased risk of thyroid cancer in a Scandinavian retrospective cohort study using an active-active comparator new user design with propensity score weighting. In the primary analysis that compared 145,410 GLP-1RA users to 291,667 dipeptidyl peptidase 4 (DPP4) inhibitor users, after a mean follow-up time of approximately 4–5 years, the incidence rates were 1.33 and 1.46 events per 10,000 person-years, respectively (HR 0.93, 95% CI 0.66-1.31). The hazard ratio for MTC was 1.19 (95% CI 0.37-3.86). In an additional analysis comparing GLP-1RA use to SGLT2i use, the hazard ratio for thyroid cancer was 1.16 (95% CI 0.65-2.05).[14] Finally, in the most robust observational study thus far, Baxter et al. performed a pooled international cohort study using databases from six countries, including Canada. Patients with T2DM were studied from 2007 to 2023, and 98,147 GLP-1RA users with a median follow-up of 1.8 to 3.0 years were compared to 99,870 DPP4 inhibitor users using propensity score weighting. GLP-1RA use was not associated with an increased risk of thyroid cancer (adjusted HR 0.81, 95% CI 0.59–1.12).[15]

Results of the observational studies are inconsistent, with the studies by Funch, Wang, and Bezin each demonstrating a statistically significant increase in GLP-1RA-associated thyroid cancer, while 5 other studies did not show significance and had variable effect sizes (**Figure 1**). However, these observational studies have limitations that make conclusions impossible, including the potential for unmeasured or residual confounding (e.g., family history, obesity, radiation exposure), detection bias, and time-related bias. Relatively short follow-up times may also be a limiting factor in observational studies of drug-induced cancer risk. In fact, the onset of thyroid cancer after only one-to-three years[8] or five years[12] of GLP-1RA exposure suggests that residual confounding or

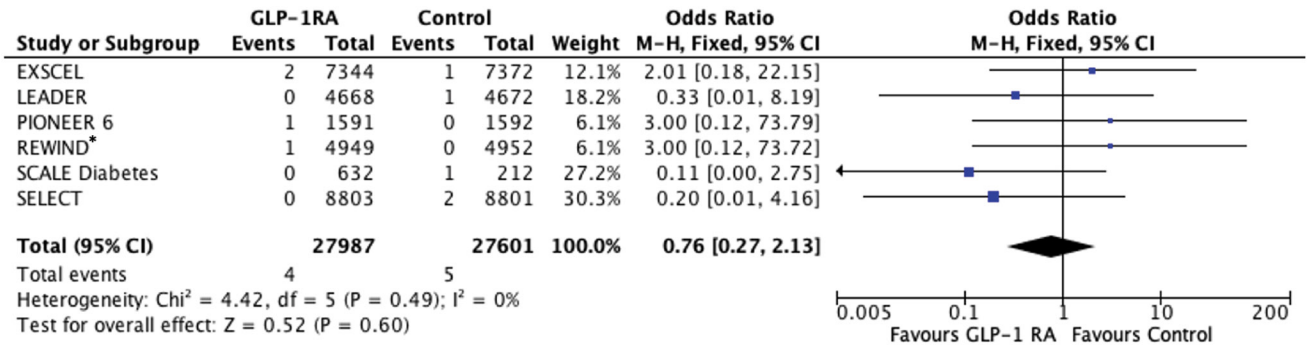

Figure 2. Meta-analysis of GLP-1RA randomized controlled trials and risk of medullary thyroid cancer; *courtesy of Ronald M, Goldenberg, MD, FRCPC, FACE*.

***The case shown in REWIND had C-cell hyperplasia and not medullary thyroid carcinoma.

Abbreviations: GLP-1RA: glucagon-like peptide-1 receptor agonist, **M-H:** Mantel–Haenszel, **CI:** confidence interval.

detection bias was present. A further limitation of the Bezin study regarding an increased risk of MTC relates to the definition of MTC that may have led to overestimation of this diagnosis, perhaps explaining the 15.5% prevalence of MTC amongst all thyroid cancer cases despite the fact that MTC should typically be observed in approximately 3% of thyroid cancer cases.[16]

Randomized Controlled Trials

It is well established that RCTs do not have the limitations or biases seen in observational studies and hence are useful in the assessment of important safety concerns such as GLP-1RA related thyroid cancer. A recent meta-analysis included all RCTs of at least 52 weeks duration that compared a European Medicines Agency approved GLP-1RA to any comparator.[17] A fixed-effect analysis of 26 trials that reported at least one incident case of thyroid cancer reported a statistically significant increase in thyroid cancer (OR 1.52, 95% CI 1.01–2.29; p=0.04). Thyroid cancer incidence was low, with only 86 cases of thyroid cancer amongst 69,909 patients. The small number of thyroid cancer cases accounted for a low fragility index, suggesting that only one additional case of thyroid cancer in the comparator arm would lead to a statistically insignificant result. In random-effect and continuity correction analyses the result was no longer significant.[17]

The potential association between GLP-1RAs and MTC has also been studied in RCTs. In large GLP-1RA outcome trials, there was no difference in calcitonin concentrations or the proportion of individuals with clinically concerning calcitonin elevations between GLP-1RA and placebo.[18,19] Cases of MTC in the GLP-1RA trials were extremely rare. In an updated meta-analysis performed by this author for this review, only six trials reported at least one case of MTC,[20-25] with 4 cases out of 27,987 individuals in the GLP-1RA arms and 5 cases out of 27,601 individuals in the comparator arms (OR 0.76, 95% CI 0.27–2.13; p=0.60) (**Figure 2**). The low incidence of MTC in the RCTs is consistent with the low incidence rate of MTC in the US population of 0.225 per 100,000 person-years.[26]

The RCTs have not proven an association between GLP-1RAs and thyroid cancer. Case numbers are relatively small with high fragility, resulting in inconclusive results.

Conclusion

The totality of evidence from pharmacovigilance, observational, and randomized controlled studies has not conclusively demonstrated a link between increased thyroid cancer and GLP-1RA treatment in humans. Although rodent studies have demonstrated an increased risk of MTC, the data in humans remains uncertain. A safety committee of the European Medicines Agency has suggested that the current evidence does not support a link between the use of GLP-1RAs in humans and thyroid cancer.[27]

Clinicians should continue prescribing GLP-1RAs for the management of T2DM or obesity when indicated as the proven benefits outweigh the unproven risk of thyroid cancer.

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