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GLP-1 RECEPTOR AGONISTS AND THYROID DISEASE: FROM MECHANISM TO CLINICAL PRACTICE

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are prescribed across type 2 diabetes, obesity, and cardiovascular indications (Drucker, 2024). Despite rodent C-cell hyperplasia with MTC/MEN2 black-box contraindication, clinical thyroid risk remains incompletely defined. This review addresses: cancer risk beyond the rodent signal, levothyroxine-treated patient hormone modulation, autoimmune thyroid natural history, and dual/triple incretin agonist profiles.

Methods. PubMed/MEDLINE, Embase, Web of Science, Cochrane CENTRAL were searched in 2025–2026 with no lower date restriction; pharmacovigilance and cohort studies were appraised for channeling bias (Sender & Stürmer, 2022).

Findings. Receptor mapping finds absent GLP-1R in normal human C-cells (Waser et al., 2014); primate toxicology at ~500× maximum human dose shows no C-cell phenotype (Knudsen et al., 2010; Vahle et al., 2015). RCT meta-analysis shows composite signal (RR 1.28, 95% CI 1.03–1.60) without individual sub-domain effects (Hu et al., 2022); cancer-specific MH-OR 1.52 (1.01–2.29), fragility index 1 (Silverii et al., 2023). FAERS class ROR 21.80 (10.25–46.36) is hypothesis-generating (Makunts et al., 2023). Baxter 2025 active-comparator cohort: HR 0.81 (0.59–1.12) (Baxter et al., 2025); vs Bezin's aHR 1.58 (1.27–1.95) with non-user comparator (Bezin et al., 2022). Class-wide thyrotropic modulation: oral semaglutide increases levothyroxine exposure ~33% (Hauge et al., 2021) with weight-loss-independent TSH reduction (Konopka et al., 2024; Sencar et al., 2019; Yu et al., 2023). Autoimmune evidence is hypothesis-generating (Jung et al., 2025; Mazokopakis, 2023; Mazza, 2025; Sabudin et al., 2025; Shlomov et al., 2026; Yaribeygi et al., 2024). Tirzepatide: SURMOUNT-3 reports 1.7% vs 1.0% malignancy, no related MTC (Wadden et al., 2023); retatrutide phase 2 endpoints unreported.

Conclusion. Modest composite thyroid signal without established cancer effect; class-wide thyrotropic modulation requiring 6–8-week levothyroxine monitoring; hypothesis-generating autoimmune signals warranting informed-consent discussion. Current regulatory framework (Watts et al., 2025) is supported.

KEYWORDS

Glucagon-like Peptide-1 Receptor Agonists, Thyroid Function Tests, Medullary Thyroid Carcinoma, C-cell Hyperplasia, Autoimmune Thyroid Disease, Pharmacoepidemiology

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Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are now prescribed across an expanding set of cardiometabolic indications: type 2 diabetes, obesity, secondary cardiovascular prevention (semaglutide, liraglutide), chronic kidney disease (semaglutide), metabolic dysfunction–associated steatotic liver disease, and obstructive sleep apnea (tirzepatide). Major outcomes programs — LEADER (liraglutide), SUSTAIN-6 (subcutaneous semaglutide), PIONEER-6 (oral semaglutide), SELECT (semaglutide in obesity without diabetes), and the SURMOUNT program for tirzepatide — have established cardiovascular, renal, and metabolic benefits, while phase 2 data on the triple incretin agonist retatrutide have demonstrated weight reduction exceeding 20% of body weight. This trajectory places a drug class carrying a long-standing thyroid-related regulatory precaution into populations whose cumulative exposure substantially exceeds that originally anticipated when the boxed warnings were drafted.

Regulatory labeling of several GLP-1RAs carries a contraindication or special precaution in patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, based upon dose- and duration-dependent C-cell hyperplasia, calcitonin elevation, and rare C-cell tumors in rodents exposed long-term to suprapharmacologic doses (Drucker et al., 2010; Knudsen et al., 2010; Madsen et al., 2012). However, this rodent-derived precaution rests on a body of subsequent evidence that fails to reproduce the effect in primates: a 52-week dulaglutide study in male cynomolgus monkeys at plasma concentrations approximately 500-fold human therapeutic exposure produced no significant calcitonin elevation, no thyroid histologic changes, and no C-cell proliferation (Vahle et al., 2015). The LEADER cardiovascular outcomes trial, with median 3.8-year follow-up, found no detectable between-arm difference in serum calcitonin or C-cell malignancy incidence at any time point (Hegedüs et al., 2017). The interpretive tension between rodent toxicology, primate counter-evidence, and long-term human trial data defines the central uncertainty in this domain.

Three specific developments have made the regulatory position increasingly clinically consequential. First, randomized controlled trial meta-analyses have reported a composite signal of increased thyroid disorders with GLP-1RA exposure, while active-comparator cohort studies have produced widely divergent estimates on cancer endpoints — a French national registry analysis found an adjusted hazard ratio of 1.58 (95% CI 1.27–1.95) for all thyroid cancer and 1.78 (95% CI 1.04–3.05) specifically for medullary thyroid carcinoma after 1–3 years of cumulative exposure, whereas an international multisite cohort pooling data from six population-based databases found no statistically significant overall thyroid-cancer signal (HR 0.81, 95% CI 0.59–1.12) (Baxter et al., 2025; Bezin et al., 2022). These divergent cohort signals reflect the role of comparator choice and channeling by indication in shaping observed estimates (D’Arcy et al., 2018; Sendor & Stürmer, 2022; Thompson & Stürmer, 2022). Second, separate from carcinogenesis, two convergent lines of evidence indicate that GLP-1RA initiation produces pharmacologically meaningful thyrotropic effects in levothyroxine-treated patients — a pharmacokinetic interaction of approximately 33% on levothyroxine exposure with oral semaglutide via delayed gastric emptying, and a body-mass-index-independent decrease in TSH of approximately 0.3 mIU/L across agents (Hauge et al., 2021; Konopka et al., 2024; Sencar et al., 2019; Yu et al., 2023). Third, GLP-1RA-induced enhancement of regulatory T-cell function and suppression of pro-inflammatory cytokines has raised theoretical concerns about perturbation of established autoimmune thyroid disease, supported by case-series-level signals in Graves’ orbitopathy and emerging autoimmune thyroiditis (Jung et al., 2025; Mazza, 2025; Shlomov et al., 2026; Yarıbeygi et al., 2024).

The convergence of high cumulative population exposure and persistent uncertainty across these three domains — carcinogenesis, functional thyroid homeostasis, and autoimmunity — defines a clinical guidance gap. Existing narrative reviews and recent position statements have addressed discrete components of this

problem in isolation, most recently the 2025 British multidisciplinary joint statement clarifying the regulatory framework for known or suspected MTC or MEN2 (Watts et al., 2025). This review addresses the gap by integrating receptor-biology, preclinical, controlled trial, pharmacovigilance, and cohort evidence with operational clinical management frameworks. Four clinically actionable thyroid subgroups structure the review: patients with no prior thyroid diagnosis, levothyroxine-treated hypothyroidism, established autoimmune thyroid disease, and identified thyroid nodules. The review addresses four corresponding questions: (a) whether real-world cumulative GLP-1RA exposure is associated with MTC risk beyond the regulatory rodent signal; (b) how clinicians should monitor and adjust levothyroxine therapy during the initiation phase in patients with pre-existing hypothyroidism; (c) whether GLP-1RAs modify the natural history of autoimmune thyroid disease, including Graves' orbitopathy and Hashimoto's thyroiditis; and (d) whether dual and triple incretin agonists (tirzepatide, retatrutide) carry distinct thyroid risk profiles from selective GLP-1RAs. A structured literature search strategy and selection criteria are described in the Methodology section.

Methodology

This is a structured narrative review synthesizing mechanistic, preclinical, clinical, pharmacovigilance, and observational evidence on glucagon-like peptide-1 receptor agonists and thyroid disease. A narrative design was chosen over formal meta-analysis because heterogeneous study designs, outcome definitions, and reporting metrics cannot be validly pooled without loss of fidelity (González-González et al., 2019; Tobias et al., 2023).

A structured search of PubMed/MEDLINE, Embase, Web of Science, and the Cochrane Library through June 2026 (no lower date restriction) was supplemented by hand-searching of reference lists, the 2025 BSE/BTA/BAETS position statement, and FDA/EMA product labeling (Watts et al., 2025). Search terms combined drug-class identifiers and individual agent names (exenatide, liraglutide, dulaglutide, semaglutide, tirzepatide, retatrutide) with thyroid-related terminology and were iteratively expanded as new literature appeared (Hu et al., 2022).

Eligible evidence comprised RCTs with thyroid endpoints (≥ 24 weeks); meta-analyses pooling such trials (Hu et al., 2022; Silverii et al., 2023); active-comparator new-user observational cohorts (Baxter et al., 2025; Pasternak et al., 2024); FAERS disproportionality analyses (Makunts et al., 2023); chronic rodent and non-human primate toxicology programs; human receptor-mapping studies; mechanistic in vitro thyroid cell-line work; and relevant regulatory documents (Smits & Raalte, 2021; Tobias et al., 2023). Case reports served only as hypothesis-generating evidence.

Methodological quality was appraised per design: RCTs via Cochrane Risk of Bias with the González-González endocrine trustworthiness framework — recognizing that only approximately 40% of endocrine-domain RCTs are adequately protected from bias (González-González et al., 2019); observational cohorts via active-comparator new-user design principles (D'Arcy et al., 2018; Sendor & Stürmer, 2022); and pharmacovigilance analyses with attention to absent denominators, channeling bias, and notoriety bias (Gibbons et al., 2010; Makunts et al., 2023).

Evidence was synthesized hierarchically across four tiers: receptor-mapping and preclinical toxicology (Boess et al., 2013; Knudsen et al., 2010; Vahle et al., 2015; Waser et al., 2014); RCT meta-analyses (Hu et al., 2022; Silverii et al., 2023; Tobias et al., 2023); active-comparator new-user cohorts (Baxter et al., 2025; Pasternak et al., 2024; Sendor & Stürmer, 2022); hypothesis-generating pharmacovigilance analyses (Gibbons et al., 2010; Makunts et al., 2023). This ordering reflects the causal-inference hierarchy appropriate to cancer-endpoint assessment under channeling-by-indication susceptibility (Thompson & Stürmer, 2022).

Three methodological limitations apply: single-reviewer screening rather than independent dual screening per PRISMA protocol; no formal publication-bias assessment given design heterogeneity; and the four-tier synthesis reflects a defensible but not unique interpretive weighting (Sendor & Stürmer, 2022; Thompson & Stürmer, 2022; Tobias et al., 2023).

Results

Mechanism of Action and Receptor Expression Analysis

GLP-1R biology and cell signaling

Glucagon-like peptide-1 is a 30-amino-acid incretin hormone secreted by intestinal L-cells in response to nutrient ingestion. Native GLP-1 has a circulatory half-life of only one to two minutes because of rapid N-terminal cleavage by dipeptidyl peptidase-4 between Ala-8 and Glu-9. The hormone exerts its effects through a single receptor, GLP-1R, a class B1 seven-transmembrane G-protein-coupled receptor whose amino acid sequence is approximately 90% conserved across mammalian species. GLP-1R couples preferentially to G α s, activates adenylyl cyclase, raises intracellular cyclic adenosine monophosphate, and engages protein kinase A and downstream effectors that drive insulin exocytosis from pancreatic β -cells, glucagon suppression, deceleration of gastric emptying, and central satiety signaling.

GLP-1RA class pharmacology

Therapeutic GLP-1RAs overcome the short half-life of native GLP-1 through structural modifications that confer DPP-4 resistance while preserving receptor engagement. Exenatide, the first clinically successful agent, is a 39-amino-acid peptide isolated from Gila monster saliva, sharing 53% sequence homology with mammalian GLP-1 and bearing an N-terminal glycine substitution that prevents DPP-4 cleavage. All subsequent approved agents retain this strategy: liraglutide, dulaglutide, albiglutide, and semaglutide substitute the DPP-4-sensitive Ala-8 residue and add fatty-acid acylation or larger protein fusions to extend plasma half-life from minutes to days. Long-acting once-weekly agents (semaglutide, dulaglutide) produce more profound effects on fasting glucose, HbA1c, and body weight, while shorter-acting agents (twice-daily exenatide) retain more pronounced and durable effects on gastric emptying. Semaglutide is uniquely available in both subcutaneous and oral formulations, with oral bioavailability enhanced by an absorption-promoting sodium N-(8-[2-hydroxybenzoyl] amino) caprylate excipient. Dual and triple incretin co-agonists such as tirzepatide and retatrutide extend this platform by incorporating GIP and glucagon receptor activity into the same peptide backbone. Half-lives span approximately 2.4 hours for exenatide (twice-daily), 13 hours for liraglutide (daily), and 4.7–7 days for dulaglutide, semaglutide, tirzepatide, and retatrutide (once-weekly). Key structural modifications include the Aib-8 substitution in liraglutide coupled with a C16 fatty-acid acyl chain, the IgG4 Fc fusion in dulaglutide, and the combined C18 fatty diacid and DPP-4-resistant linker in semaglutide (Hu et al., 2022; Smits & Raalte, 2021).

Tissue distribution of GLP-1R beyond the thyroid

GLP-1R is broadly distributed across tissues relevant to the metabolic and cardiovascular actions of the drug class: pancreatic β -cells, vascular smooth muscle, renal arterioles, sinoatrial-node cardiomyocytes, Brunner's glands of the duodenum, gastric parietal cells, myenteric plexus neurons, and key central nervous system regions including the hypothalamus and the nucleus of the solitary tract. Using a rigorously validated monoclonal antibody applied to monkey and human tissue, Pyke and colleagues found no GLP-1R immunoreactivity in primate or human hepatocytes, while establishing robust expression in pancreatic islets, Brunner's glands, and the vascular smooth muscle of systemic arteries (Pyke et al., 2014). This broad tissue distribution underlies the pleiotropic metabolic effects of the class — HbA1c reductions of approximately 1–1.5 percentage points, weight loss ranging from 5% to more than 20% depending on dose, and reductions in major adverse cardiovascular events of 14–21% — and explains why extrathyroid receptor mapping of GLP-1R has been biased increasingly toward these cardiometabolic targets (Smits & Raalte, 2021; Tobias et al., 2023).

Species-specific thyroid receptor distribution

The thyroid question turns on a discrete cellular subset: parafollicular C-cells, the calcitonin-producing cells from which medullary thyroid carcinoma arises. The translational literature on this question is genuinely discordant, and the discordance derives in substantial part from antibody-specificity differences among immunohistochemistry reagents. Studies using validated monoclonal antibodies or quantitative receptor autoradiography — methods less vulnerable to nonspecific staining — generally find GLP-1R expression in normal human thyroid tissue to be absent-to-marginal. Waser and colleagues, who combined immunohistochemistry with quantitative ¹²⁵I-labeled GLP-1 receptor autoradiography, found that none of eight normal thyroid specimens expressed detectable GLP-1R using either method, that none of eight C-cell hyperplasia specimens were positive, and that zero of eight papillary thyroid carcinoma specimens were positive; among medullary thyroid carcinoma specimens, only 2 of 10 sporadic cases and 0 of 10 MEN2-associated cases showed specific binding above background (Waser et al., 2014). By contrast, studies using older polyclonal antisera report widely varying expression. Gier and colleagues reported that approximately 33% of normal thyroid specimens showed detectable GLP-1R immunoreactivity, with increased immunoreactivity in medullary thyroid carcinoma specimens (Gier et al., 2011). Jung and Kwon also used polyclonal immunohistochemistry and reported variable but generally detectable expression in papillary thyroid carcinoma specimens (Jung & Kwon, 2014). Song and colleagues reported GLP-1R positivity in 33.3% of normal human thyroid tissue, 100% of C-cell hyperplasia specimens, and 100% of MTC specimens (Song et al., 2017).

The functional corollary of these divergent mapping results has been tested directly in primary C-cell culture. Boess and colleagues established paired primary cultures of rat and human C-cells and exposed them to high concentrations of tasoglutide or liraglutide. The rat C-cells expressed GLP-1R and released calcitonin in response to stimulation; the human primary C-cells expressed no detectable GLP-1R and released no calcitonin in response to either agent (Boess et al., 2013). The functional data therefore corroborate the receptor-mapping data generated by validated methods: the rodent C-cell model exhibits the proliferative response that anchors the regulatory concern, while primary human C-cells in vitro do not. This species-specific divergence is the proximal molecular basis on which the entire rodent-to-human extrapolation debate rests.

Preclinical Evidence

The preclinical evidence base on GLP-1RA thyroid safety comprises three qualitatively distinct streams that point in different directions: rodent carcinogenicity studies (reproducibly positive), non-human primate chronic toxicology studies (reproducibly null), and in vitro tumor cell-line studies (counter-directional antiproliferative signal).

Rodent carcinogenicity

Chronic rodent carcinogenicity studies, submitted as part of regulatory registration dossiers across all approved GLP-1RAs, demonstrate a uniform dose-dependent phenotype: increases in circulating calcitonin and thyroid weight, diffuse C-cell hyperplasia, focal C-cell adenoma formation, and an increased incidence of medullary thyroid carcinoma. As Drucker and colleagues summarized the early regulatory experience, the class effect was observed across multiple agents and was both dose-dependent and exposure-time-dependent (Drucker et al., 2010). Knudsen and colleagues established that the C-cell response is mediated through a cAMP-dependent pathway activating GLP-1R on parafollicular C-cells (Knudsen et al., 2010). Mechanistic specificity was confirmed in Glp1r-knockout mice, which failed to develop any C-cell pathology on identical liraglutide exposure — establishing that the rodent C-cell response is receptor-mediated and not a generic effect of the drug on thyroid tissue. Pharmacodynamic analyses from the Knudsen study showed that receptor occupancy — rather than plasma drug concentration — was the more robust predictor of C-cell hyperplasia, with the threshold for triggering C-cell hyperplasia in rats at daily liraglutide doses producing human plasma equivalents well above any approved human dosing (Hu et al., 2022; Madsen et al., 2012). Byrd and colleagues' chronic rodent toxicology program for dulaglutide replicated the canonical C-cell phenotype across multiple rodent species, dose levels, and exposure windows (Byrd et al., 2015).

Non-human primate chronic toxicology

The translational counter-evidence comes from chronic toxicology studies in cynomolgus monkeys at exposures far exceeding the maximum recommended human dose. The seminal primate study treated monkeys with liraglutide at more than 60-fold the human plasma exposure for 20 months: no C-cell hyperplasia developed, no adenylate cyclase activation occurred in primate C-cells, and mean calcitonin remained within normal limits (Knudsen et al., 2010). The dulaglutide primate carcinogenicity study replicated this null finding using a molecularly distinct agent: 52 weeks of dulaglutide at 8.15 mg/kg twice weekly — approximately 500-fold the maximum recommended human plasma exposure — produced no alterations in absolute or relative C-cell volume, no Ki67 labeling change, no thyroid-weight or histology change, and no elevation of either basal or calcium-stimulated calcitonin at months 3, 6, 9, or 12 (Vahle et al., 2015). The breadth of species — mouse, rat, and non-human primate — combined with duration of exposure and magnitude of dose multiples collectively represent the empirical foundation on which regulatory judgments about clinically relevant carcinogenicity risk have rested.

In vitro tumor cell-line antiproliferative counter-signal

A distinct preclinical stream indicates that, where GLP-1R is expressed at sufficient density in human thyroid tumor cells, receptor activation may exert antiproliferative rather than proliferative effects. Zhang and colleagues engineered human TT medullary thyroid carcinoma cells and TCP-1 papillary thyroid carcinoma cells to stably overexpress GLP-1R and exposed them to increasing concentrations of liraglutide. They observed a dose- and time-dependent inhibition of both cell proliferation and migration, accompanied by reduced phosphorylation of Akt, S6K1, and 70S6K, consistent with suppression of the PI3K/Akt/mTOR pathway — a finding that argues against the default assumption that receptor activation, where it occurs at sufficient density, must recapitulate the rodent proliferative phenotype (Zhang et al., 2023).

Synthesis

The three preclinical streams converge on a single interpretive framework: the rodent C-cell response is real, GLP-1R-mediated, and conditionally expressed; it does not extend to primates at clinically relevant exposures; and where human tumor cells express GLP-1R at sufficient density, receptor activation appears more likely to inhibit than to promote proliferation. This framework provides the empirical basis for both the FDA boxed warning for medullary thyroid carcinoma and multiple endocrine neoplasia type 2 and the unresolved clinical questions examined in the subsequent sections.

C-cell Proliferation Markers

The regulatory and clinical interpretation of GLP-1RA thyroid safety depends on three principal categories of biomarker, each with characteristic strengths and inherent limitations.

Serum calcitonin is the most consistently applied biomarker across the development program. In the LEADER cardiovascular outcome trial — with a dedicated calcitonin substudy and patient-level data spanning up to five years of exposure — liraglutide produced no detectable rise in either basal or stimulated calcitonin and no C-cell malignancies in the active arm (Hegedüs et al., 2017; Smits & Raalte, 2021). In the SUSTAIN phase 3 program, with a combined safety population of 5,933 semaglutide-treated patients versus 4,736 comparators, there was no notable difference in mean serum calcitonin across treatment arms (Smits & Raalte, 2021). The clinical relevance of any individual elevated calcitonin value must be interpreted against the rarity of medullary thyroid carcinoma, which has a population-level incidence ranging from 0.14 to 0.21 per 100,000 per year (Garo et al., 2022; Smits & Raalte, 2021). This rare-event biology makes statistical detection of even a moderate drug-induced signal in pre-approval trials effectively impossible — a 5,000-patient development program accumulates less than one expected MTC event from background incidence alone.

Tissue-level C-cell metrics in preclinical toxicology, including C-cell volume, Ki67 labeling index, and serial serum calcitonin with calcium stimulation, provide the principal quantitative readout for the rodent-versus-primate comparison. The dulaglutide primate study provides the cleanest null phenotype reported for

any GLP-1RA chronic toxicology program: at approximately 500-fold the maximum recommended human plasma exposure across 52 weeks, no alteration in any of these C-cell metrics was detected (Vahle et al., 2015).

Clinical MTC incidence is the ultimate integrative biomarker reflecting the cumulative effect of any cell-biological, marker-based, or subclinical C-cell alteration. The combination of rare-event biology, a specific but low-sensitivity serum biomarker, the absence of validated imaging-based C-cell mass measurements in clinical practice, and the lack of standardized reporting thresholds across laboratories means that this biomarker set is inherently insensitive to a low-magnitude drug effect that might operate over decades of cumulative exposure.

Clinical Observations

Randomized controlled trial meta-analytic evidence

The randomized controlled trial evidence on GLP-1RA thyroid safety is best understood by separating aggregate meta-analyses from their non-replicating sub-components. Two principal meta-analyses have been published, with results that diverge sharply on the most clinically important endpoint.

The first, more comprehensive meta-analysis by Hu and colleagues pooled 45 randomized trials encompassing 94,063 patients and identified a 28% relative increase in overall composite thyroid disorders with GLP-1RA exposure, with a pooled risk ratio of 1.28 (95% confidence interval 1.03 to 1.60, $p = 0.027$) (Hu et al., 2022). No between-study heterogeneity was detected ($I^2 = 0.0\%$), and no statistically significant effect emerged on any individual thyroid sub-category: hypothyroidism yielded a pooled RR of 1.22 (95% CI 0.80 to 1.87), hyperthyroidism yielded 1.19 (95% CI 0.61 to 2.35), thyroiditis yielded 1.83 (95% CI 0.51 to 6.57), thyroid mass yielded 1.17 (95% CI 0.43 to 3.20), goiter yielded 1.17 (95% CI 0.74 to 1.86), and thyroid cancer yielded 1.30 (95% CI 0.86 to 1.97).

Statistically significant sub-agent effects were confined to liraglutide and dulaglutide. For liraglutide, based on 18 trials encompassing 24,787 patients ($I^2 = 0\%$), the agent-specific pooled risk ratio for overall thyroid disorders was 1.37 (95% CI 1.01 to 1.86, $p = 0.044$). For dulaglutide, based on 5 trials encompassing 13,281 patients, the agent-specific pooled risk ratio was 1.96 (95% CI 1.11 to 3.45, $p = 0.020$). By contrast, no statistically detectable effect was found for exenatide (RR 0.82, 95% CI 0.21 to 3.29), semaglutide (RR 0.75, 95% CI 0.35 to 1.57), lixisenatide, or albiglutide (RR 0.76, 95% CI 0.31 to 1.83) (Hu et al., 2022).

The second principal meta-analysis, by Silverii and colleagues, was structured around the cancer endpoint specifically. Of 64 trials overall encompassing 84,627 patients, 26 trials with at least 52 weeks of follow-up reported at least one thyroid cancer case. Across these 26 trials with 46,228 GLP-1RA-treated patients and 38,399 comparator patients, 86 thyroid cancer events occurred (60 in active arm, 26 in comparator), of which 25 were papillary thyroid carcinoma and 3 were medullary thyroid carcinoma. The pooled Mantel–Haenszel odds ratio for thyroid cancer overall was 1.52 (95% CI 1.01 to 2.29, $p = 0.04$), with no between-study heterogeneity ($I^2 = 0\%$). This pooled effect estimate carried a fragility index of only one — meaning that converting the status of one single event from "event" to "non-event" would collapse the result to non-significance — with a corresponding 5-year number-needed-to-harm of 1,349 patients. Histology-specific estimates for papillary thyroid carcinoma (MH-OR 1.54, 95% CI 0.77 to 3.06) and medullary thyroid carcinoma (MH-OR 1.44, 95% CI 0.23 to 9.16) remained non-significant. In a sensitivity analysis restricted to trials with at least 104 weeks of follow-up, the pooled Mantel–Haenszel odds ratio for thyroid cancer rose to 1.76 (95% CI 1.00 to 3.12, $p = 0.05$) (Hegedüs et al., 2017; Silverii et al., 2023). The discordance between the two meta-analyses is most plausibly attributable to trial-duration filtering, with the Silverii synthesis applying a ≥ 52 -week duration filter that substantially increases cancer event counts relative to the shorter-duration trial set pooled in Hu.

Within-trial thyroid-event enumeration

The principal cardiovascular outcome trials and registration programs reported small absolute numbers of adjudicated thyroid events. In the LEADER cardiovascular outcomes trial for liraglutide with median 3.8-year follow-up, encompassing over 9,000 patients, no medullary thyroid carcinoma occurred in the active arm and no C-cell malignancy emerged in either arm; mean basal calcitonin levels showed no between-arm difference at any timepoint (Hegedüs et al., 2017; Smits & Raalte, 2021). In the SUSTAIN phase 3 program combined with SUSTAIN-6, encompassing 5,933 semaglutide-treated patients versus 4,736 comparators, three adjudicated events of malignant thyroid neoplasm occurred (2 in semaglutide-treated patients, 1 in comparator), and none was medullary in origin (Smits & Raalte, 2021). In the PIONEER oral semaglutide program, four thyroid malignancies occurred in semaglutide-treated patients versus one in the comparator arm, including one medullary thyroid carcinoma case that developed in a patient with pre-existing nodules and elevated baseline calcitonin (Smits & Raalte, 2021).

Pharmacovigilance signal-detection evidence

Spontaneous-reporting analyses based on the FDA Adverse Event Reporting System and equivalent databases provide a distinct profile, capturing the kind of aggregate signal that pre-approval randomized programs under-power against. Makunts, Joulfayan, and Abagyan's analysis of FAERS data encompassing 17,653 GLP-1RA monotherapy reports and 14,102 SGLT-2 inhibitor monotherapy reports identified 191 unique thyroid-hyperplasia/neoplasm adverse-event reports in the GLP-1RA group versus 7 in the SGLT-2 group, generating a class-level reporting odds ratio of 21.80 (95% CI 10.25 to 46.36) (Makunts et al., 2023). Agent-specific reporting odds ratios were markedly heterogeneous: liraglutide carried the largest reported odds ratio at 35.31 (95% CI 16.43 to 75.88), generated from 108 hyperplasia/neoplasm reports in a cohort with a mean age of 53.07 ± 11.08 years and female predominance of 66; semaglutide generated 33 events with a reporting odds ratio of 20.58 (95% CI 9.19 to 46.57); dulaglutide generated 33 events with a reporting odds ratio of 17.60 (95% CI 7.80 to 39.92); exenatide generated 17 events with the smallest agent-level reporting odds ratio at 7.62 (95% CI 3.16 to 18.39) and a notably older mean cohort age of 64.67 ± 6.35 years (Makunts et al., 2023).

This agent ranking does not reproduce the Hu 2022 sub-group result. This non-concordance is most parsimoniously attributed to channeling bias, media-driven reporting surges following regulatory communications, and confounding by indication, and is best adjudicated using active-comparator new-user designs that neutralize prevalent-user bias and allow for prespecified lag periods (D'Arcy et al., 2018; Gibbons et al., 2010; Makunts et al., 2023; Sendor & Stürmer, 2022).

Real-world active-comparator cohort evidence

The active-comparator new-user observational cohort evidence base has now reached a scale that meaningfully addresses the randomized-trial under-powering problem for rare cancer endpoints.

The Baxter 2025 international multisite cohort, encompassing 98,147 GLP-1RA users and 2,488,303 DPP-4 inhibitor users across six population-based databases, with median GLP-1RA follow-up between 1.8 and 3.0 years, reported a pooled weighted hazard ratio of 0.81 (95% CI 0.59 to 1.12) using standardized mortality ratio weighting of time-specific propensity scores, providing no evidence of an increased thyroid-cancer risk and no cumulative dose-response gradient (Baxter et al., 2025).

The Pasternak 2024 Scandinavian cohort, with comparable design and a mean follow-up of 3.9 years, found that GLP-1RA exposure was not associated with a substantially increased risk of thyroid cancer, with an upper confidence limit consistent with no more than a 31% relative risk increase (Pasternak et al., 2024).

A Korean National Health Insurance claims cohort using SGLT2 inhibitors as active comparators produced a weighted hazard ratio of 0.98 (95% CI 0.62 to 1.53), paralleling the Baxter and Pasternak null results (Capuccio et al., 2024).

The Bezin 2022 French National Healthcare Insurance System nested case-control study, encompassing 2,562 thyroid cancer cases matched to 45,184 controls, contained a positive observational signal that sits in tension with the contemporary active-comparator null results: one to three years of GLP-1RA exposure was associated with an adjusted hazard ratio of 1.58 (95% CI 1.27 to 1.95) for all thyroid cancer and 1.78 (95% CI 1.04 to 3.05) for medullary thyroid carcinoma specifically (Bezin et al., 2022; Thompson & Stürmer, 2022). The Bezin study used a non-user comparator rather than the active-comparator new-user design deployed in Baxter and Pasternak, and the divergence is most plausibly attributable to this design difference — and specifically to inadequate control of channeling bias and confounding by indication (D'Arcy et al., 2018; Sendor & Stürmer, 2022).

TSH-stability evidence in levothyroxine-treated patients

A distinct and clinically actionable evidence stream concerns GLP-1RA effects on thyroid hormone economy in patients on stable levothyroxine replacement. Four convergent lines of evidence support the existence of pharmacologically meaningful post-initiation thyrotropic effects in this subpopulation.

A pharmacokinetic interaction has been characterized. The Hauge and colleagues open-label crossover study established that oral semaglutide co-administration increases levothyroxine exposure by approximately 33% via delayed gastric emptying, providing a directly quantified pharmacokinetic mechanism (Hauge et al., 2019, 2021).

Retrospective cohort data on tirzepatide have generated preliminary clinical signal. Yu and colleagues' review of 17 levothyroxine-stable tirzepatide-treated patients found TSH suppression below the normal range in 5 patients (29% of the cohort) and any TSH reduction in 11 patients (65%) within a mean follow-up of 53.3 days and a median of 47 days — substantially before the typical time point at which tirzepatide-induced weight loss plateaus (Yu et al., 2023).

Prospective modulation data on the broader hypothalamic-pituitary-thyroid axis have been generated. The Konopka 2024 three-month oral semaglutide study in 290 adults with obesity demonstrated statistically significant decreases in TSH (a reduction of 0.32 mIU/L, $p < 0.001$) and free T3 (a reduction of 0.33 pg/mL, $p < 0.001$), with both changes independent of weight loss, consistent with — though not directly establishing — direct HPT-axis modulation (Konopka et al., 2024).

The Sencar prospective exenatide study in 33 diabetic patients without prior thyroid disease demonstrated a significant decrease in serum TSH from 2.3 mIU/L at baseline to 1.8 mIU/L at six months ($p = 0.007$) without change in fT4 or fT3 and without change in thyroid volume (11.6 cm³ baseline vs. 12.1 cm³ at six months, $p = 0.19$); critically, there was no correlation between TSH variation and BMI change, suggesting a non-weight-loss-mediated mechanism (Sencar et al., 2019).

The Chen 2026 trial-emulation analysis documented that TSH testing patterns after GLP-1RA initiation do not differ from those after SGLT-2i initiation despite the greater likelihood of weight-associated levothyroxine dose adjustment with GLP-1RA therapy — identifying a monitoring gap rather than quantifying the underlying endocrine phenomenon (Chen et al., 2026).

Autoimmune thyroid disease evidence

The clinical evidence base on whether GLP-1RA exposure perturbs the natural history of autoimmune thyroid disease — Graves' disease, Hashimoto's thyroiditis, and Graves' orbitopathy — is dominated by mechanistic plausibility and case-level signals, with no prospective controlled data yet establishing causality.

Mechanistic plausibility is biologically grounded. Mazza, in a dedicated synthesis of autoimmune thyroid disease pathophysiology and GLP-1RA pharmacology, summarized that GLP-1RAs exert established immunomodulatory effects including suppression of pro-inflammatory cytokines, enhancement of regulatory T-cell function, and modulation of adipose-tissue and gut-derived immune signaling; mechanistic hypotheses invoked for thyroid-specific autoimmune impact include reduced leptin-driven T-helper 1/17 activity,

improved adipokine balance, and modulation of gut-thyroid axis pathways, with Mazza emphasizing that autoimmune thyroid disease increasingly coexists with metabolic disorders including obesity, insulin resistance, and MASLD (Mazza, 2025). These immunomodulatory axes have independent support from mechanistic reviews of semaglutide's broader anti-inflammatory profile (Yaribeygi et al., 2024), and from a case report of Sjögren's syndrome-flare suppression on semaglutide with mechanistic transferability to organ-specific autoimmunity (Jung et al., 2025). A cellular substrate on which autoimmune-mediated enhancement of C-cell activity could theoretically act is provided by Song and colleagues' documentation of concurrent expression of GLP-1R and CD26 in human thyroid C-cells, with differential density in C-cell hyperplasia and medullary thyroid carcinoma specimens (Song et al., 2017).

The clinical evidence pool remains at the case-series level. Shlomov and colleagues characterized an association between semaglutide use and thyroid-eye-disease-related outcomes in patients with autoimmune thyroiditis and type 2 diabetes, generating a clinically meaningful signal in the Graves' orbitopathy subpopulation (Shlomov et al., 2026). Counter-directionally, paradoxical thyrotoxic presentations including new-onset hyperthyroidism after liraglutide initiation with resolution upon drug discontinuation have been reported (Sabudin et al., 2025), and de novo subclinical hypothyroidism developing in patients without pre-existing thyroid disease on semaglutide is documented (Mazokopakis, 2023). The current evidence pool is best characterized as hypothesis-generating rather than confirmatory, justifying informed-consent-level discussion with patients who have active autoimmune thyroid disease rather than categorical treatment refusal (Jung et al., 2025; Mazza, 2025; Yaribeygi et al., 2024).

Dual and triple incretin agonist evidence

The dual GLP-1/GIP co-agonist tirzepatide and the triple GLP-1/GIP/glucagon co-agonist retatrutide raise a discrete thyroid question: does the addition of GIP and glucagon receptor activity to the GLP-1 backbone alter thyroid-specific safety profiles relative to selective GLP-1RAs? Three evidence streams address this question.

Within-trial cancer enumeration from phase 3 registration trials is informative for tirzepatide. In the SURMOUNT-3 tirzepatide trial, malignancies occurred in 1.7% of tirzepatide-treated participants versus 1.0% in placebo, with no cases considered related to study treatment by investigators and no medullary thyroid carcinoma or pancreatic cancer cases reported (Wadden et al., 2023). The interpretation is necessarily limited by exposure duration and the prevalence-based reporting model.

FAERS disproportionality analysis specific to tirzepatide enriches the signal-detection picture. Ou and colleagues' 2024 analysis of FAERS data for tirzepatide identified medullary thyroid cancer in 7 reports (reporting odds ratio 17.19, EBGM 3.94) and follicular thyroid cancer in 3 reports (reporting odds ratio 16.27, EBGM 3.87), with the explicit implementation in the United States of a black-box warning for thyroid C-cell tumors — a regulatory action that itself generates a post-warning notoriety-driven reporting surge that complicates signal interpretation (Ou et al., 2024). The discrepancy with SURMOUNT-3 null data reflects the same channeling-by-indication and notoriety-bias structures documented for the broader GLP-1RA class (Makunts et al., 2023; Sendor & Stürmer, 2022).

Prospective thyrotropic and inflammatory modulation data in tirzepatide-treated patients supplement the picture. The Yu retrospective cohort of 17 levothyroxine-stable tirzepatide-treated patients identified above (29% TSH suppression, 65% any TSH reduction at a mean 53.3-day follow-up) (Yu et al., 2023) is complemented by a case report of biphasic painless thyroiditis with transient thyrotoxicosis followed by hypothyroidism following two months of tirzepatide therapy, with negative thyroid autoantibodies, ultrasound heterogeneous echotexture with increased vascularity consistent with thyroiditis, and resolution of thyroid dysfunction two months after discontinuation (Humaida et al., 2025). Tirzepatide-specific chronic rodent and primate carcinogenicity programs have not been detailed in published regulatory summaries, and retatrutide phase 2 thyroid-cancer endpoint data have not yet been reported in the public peer-reviewed literature despite phase 3 trials in cardiometabolic indications now underway. This evidence gap identifies the principal route through which the dual/triple incretin agonist thyroid question will be answered over the coming decade.

Safety Profile Assessments

What the agent-specific RCT evidence shows is reassuring on carcinogenicity

For most agents, the within-program RCT evidence on thyroid neoplasia is null or contains small numbers of events whose origin is most parsimoniously attributable to underlying nodular pathology rather than drug exposure. In SUSTAIN combined with SUSTAIN-6, three adjudicated events of malignant thyroid neoplasm occurred and none was medullary in origin. In PIONEER, four thyroid malignancies occurred in semaglutide-treated patients, including one medullary thyroid carcinoma in a patient with pre-existing nodules and elevated baseline calcitonin (Smits & Raalte, 2021). In LEADER, no between-arm difference emerged in either calcitonin levels or C-cell malignancies across median 3.8-year follow-up (Hegedüs et al., 2017; Smits & Raalte, 2021). For dulaglutide, the pre-marketing primate chronic toxicology failed to alter serum calcitonin, thyroid weight, C-cell volume, or Ki67 labeling across a 52-week exposure window at approximately 500-fold human exposure (Vahle et al., 2015). Exenatide remains the agent with the most divergent FAERS-to-RCT ratio — a discrepancy that does not constitute clinical evidence of differential carcinogenicity but does motivate continued pharmacovigilance attention until active-comparator data with sufficient exenatide exposure accumulate (Hu et al., 2022; Makunts et al., 2023).

Synthesis defining the current safety profile

Four mutually constraining lines of evidence define the current thyroid-safety profile of GLP-1RAs. The first is a statistically significant but quantitatively modest composite-level signal — risk ratio of 1.28 (95% CI 1.03 to 1.60) at the overall-disorder level in the Hu 2022 meta-analysis, translating to absolute event rates of 0.39% in the GLP-1RA arms versus 0.31% in controls (a difference of approximately 0.08 percentage points) — without a statistically significant effect on any specific sub-domain individually (Hu et al., 2022). The second is a cancer-specific signal — Mantel-Haenszel odds ratio of 1.52 (95% CI 1.01 to 2.29) in the Silverii 2023 meta-analysis — that rests on a fragility index of 1 and remains agnostic on papillary and medullary thyroid carcinoma histology-specific estimates (Silverii et al., 2023). The third is a class-level FAERS reporting odds ratio of 21.80 (95% CI 10.25 to 46.36) that is appropriately interpreted as hypothesis-generating in light of channeling bias, confounding by indication, and the post-regulatory-notoriety reporting surge that spontaneously-reporting systems are structurally vulnerable to (D'Arcy et al., 2018; Makunts et al., 2023; Sendor & Stürmer, 2022). The fourth is short-term reassurance from the Baxter 2025 active-comparator multisite cohort with hazard ratio 0.81 (95% CI 0.59 to 1.12), with median follow-up insufficient to exclude effects at long exposure durations (Baxter et al., 2025). The synthesis required attending explicitly to the bias structures specific to each evidence stream: spontaneous-reporting analyses interpreted as hypothesis-generating because of channeling bias, notoriety bias, and the absence of a defined patient denominator; observational single-arm or prevalent-user cohorts interpreted as suggestive but not confirmatory because of detection bias arising from differential neck ultrasound utilization; and active-comparator, new-user cohort designs weighted as the most defensible observational evidence for short-term carcinogenicity assessment at the population scale (D'Arcy et al., 2018; Gibbons et al., 2010; Sendor & Stürmer, 2022; Thompson & Stürmer, 2022). The trustworthiness framework of González-González and colleagues was applied throughout, requiring critical appraisal of trial design rather than face-value acceptance of published estimates (González-González et al., 2019; Tobias et al., 2023).

Discussion

Clinical Practice Implications

The synthesis presented in the Results section has four principal implications for clinical practice. First, the rodent-to-human extrapolation that anchors regulatory labeling is supported by a substantive body of mechanistic and chronic-toxicology evidence rather than by clinical-trial outcome data. The Waser quantitative autoradiography and the Boess paired primary C-cell culture study both indicate that biologically meaningful GLP-1R expression is largely absent in human thyroid C-cells under representative stimulation (Boess et al., 2013; Waser et al., 2014). Second, no statistically significant effect on separate thyroid sub-conditions has yet emerged from randomized trial meta-analysis, despite a small composite-level signal that, given a fragility index of 1 in the cancer-specific pooled estimate, rests on thin absolute-event margins (Hu et al., 2022; Silverii et al., 2023). Third, the short follow-up durations of the Baxter and Pasternak active-comparator cohorts (median 1.8–3.0 years and mean 3.9 years respectively) are insufficient to exclude a low-magnitude carcinogenic effect that might require decades of cumulative exposure to manifest at the population level (Baxter et al., 2025; Pasternak et al., 2024). Fourth, the pharmacokinetic and prospective HPT-axis data from Hauge, Konopka, Yu, and Sencar indicate that GLP-1RAs exert observable thyrotropic effects across all current agents whenever they are studied carefully, even when biomarker changes do not constitute clinical adverse events individually (Hauge et al., 2019, 2021; Konopka et al., 2024; Sencar et al., 2019; Yu et al., 2023).

Pre-Treatment Patient Assessment

A reasonable practical framework for pre-treatment assessment can be derived directly from the evidence base. First, patients with a personal or family history of medullary thyroid carcinoma, multiple endocrine neoplasia type 2, or any condition for which genetic counseling for RET mutations has been recommended should not be initiated on a GLP-1RA — this remains the regulatory contraindication in current UK multidisciplinary guidance (Watts et al., 2025) and is consistent with the species-specific receptor mapping evidence (Boess et al., 2013; Waser et al., 2014). Second, a focused neck-examination-guided history establishes whether the patient has any known thyroid nodule, recent thyroid ultrasound, prior abnormal serum calcitonin, or family history of thyroid neoplasia, while routine baseline calcitonin screening of all candidates cannot be recommended on current evidence given the rarity of MTC and the lack of standardized reporting thresholds (Garo et al., 2022; Smits & Raalte, 2021). Third, patients receiving stable levothyroxine replacement should be identified at the time of prescribing and flagged for closer biochemical monitoring in the first 8–12 weeks of therapy, because pharmacokinetic and prospective modulation data suggest this is the period of greatest vulnerability (Hauge et al., 2019, 2021; Konopka et al., 2024; Sencar et al., 2019; Yu et al., 2023).

In Patients with Pre-Existing Hypothyroidism on Levothyroxine

For this substantial subpopulation, four practical implications follow from the evidence stream. Pharmacokinetic mechanism is established for oral semaglutide, where co-administration increases levothyroxine exposure by approximately 33% (Hauge et al., 2021). Prospective signals in tirzepatide (TSH suppression in 5 of 17 patients within a mean 53.3 days), oral semaglutide (TSH reduction of 0.32 mIU/L at 3 months, independent of weight loss), and exenatide (TSH reduction from 2.3 to 1.8 mIU/L at 6 months, independent of BMI change) suggest the effect is class-wide rather than agent-specific (Konopka et al., 2024; Sencar et al., 2019; Yu et al., 2023). Pragmatic monitoring, consisting of a serum TSH check approximately 6–8 weeks after any dose increase, with downward adjustment of levothyroxine when TSH trends below the patient's prior baseline, is a reasonable approach. The Chen trial-emulation finding that real-world TSH testing patterns do not yet differ between GLP-1RA and SGLT-2i initiators suggests that this pragmatic surveillance is currently under-utilized (Chen et al., 2026).

In Patients with Known or Suspected Autoimmune Thyroid Disease

The implications here are more cautious. The pool of evidence is dominated by case reports of paradoxical thyrotoxic presentations, subclinical hypothyroidism de novo, and emerging thyroid-eye-disease–related outcomes, without prospective controlled data to establish causality for autoimmune-triggering effects (Capuccio et al., 2024; Mazokopakis, 2023; Mazza, 2025; Sabudin et al., 2025; Shlomov et al., 2026). A mechanistic basis for autoimmune modulation is biologically plausible through the welldocumented immunomodulatory activity of GLP-1RAs, but at present the observations justify informed-consent-level discussion rather than categorical treatment refusal. Patients with active Graves' orbitopathy, recent-onset or unstable Hashimoto's thyroiditis, or recent thyroidectomy for autoimmune disease may reasonably be initiated on alternative anti-obesity or antidiabetic agents where clinically appropriate while active-comparator registry data mature.

In Patients with Thyroid Nodules

The most defensible interpretation is conservative. Patients with known benign-appearing nodules that have been characterized by ultrasound (and where clinically appropriate, by fine-needle aspiration) can be initiated on therapy with a documented baseline assessment, with no current evidence justifying categorical avoidance. Patients with Bethesda III/IV nodules under surveillance, nodules larger than approximately 1 cm that have not been fully characterized, or elevated baseline calcitonin warrant specialist endocrinology referral before initiation because the cancer-specificity of the underlying nodular context is the factor most likely to confound interpretation of any subsequent event. The rare-event biology of medullary thyroid carcinoma (0.14–0.21 per 100,000 per year) means that even a moderately elevated population-level hazard ratio would not translate into a meaningful absolute risk for individual nodule-bearing patients (Garo et al., 2022; Smits & Raalte, 2021).

Treatment Selection Considerations

Within the GLP-1RA class, the agent-specific evidence base does not currently justify any single agent as the preferred option on thyroid-safety grounds alone. The Hu 2022 sub-agent estimates were statistically significant for liraglutide (RR 1.37) and dulaglutide (RR 1.96) but not for semaglutide, exenatide, lixisenatide, or albiglutide, while the FAERS agent-level reporting odds ratios place liraglutide highest at 35.31 and exenatide lowest at 7.62, with divergent agent rankings between the two evidence streams (Hu et al., 2022; Makunts et al., 2023). The chronic-toxicology reassurance is strongest for dulaglutide, which has been studied in primates at approximately 500-fold the maximum human exposure for 52 weeks without detectable C-cell effect (Vahle et al., 2015). For tirzepatide, the evidence base for the thyroid-specific question is more limited, with the bulk of the prospective modulation data derived from tirzepatide-treated patients on stable levothyroxine rather than from chronic-toxicology programs (Yu et al., 2023).

Surveillance During Therapy

A pragmatic surveillance scheme responsive to the current evidence stream includes the following elements: routine annual neck palpation and clinical evaluation for any patient on long-term GLP-1RA therapy; serum TSH at 6–8 weeks after initiation or after any GLP-1RA dose escalation in patients on levothyroxine; and lower threshold for subspecialty referral for any palpable abnormality, new compressive symptom, persistent unexplained dysphagia or dysphonia, or persistent unexplained biochemical change. Routine serial calcitonin cannot be recommended on current evidence: pre-approval lifelong monitoring data show no consistent between-arm signal across the GLP-1RA development programs (Hegedüs et al., 2017; Smits & Raalte, 2021), and the substantial false-positive rate arising from non-thyroid pathology — including renal insufficiency, neuroendocrine tumors, and assay-specific variability in calcitonin reporting thresholds — would yield more harm than benefit if deployed as a general screening tool (Garo et al., 2022).

Special Populations

Pediatric, pregnant, and lactation populations remain effectively unstudied for thyroid-specific outcomes, and current product labeling — uniformly cautious — should guide decisions. Patients with renal insufficiency or hepatic impairment, who are commonly encountered in the cardiometabolic context in which GLP-1RAs are now used, do not appear to face differential thyroid risk on the current evidence base, though the pharmacokinetic sensitivity of agents metabolized or cleared through these pathways should inform agent selection on grounds independent of thyroid safety (Capuccio et al., 2024; Smits & Raalte, 2021).

Patient Communication and Summary Clinical Decision Algorithm

The clinical algorithm that condenses this discussion can be summarized in three sequential decisions. First, the patient must not have personal or family history of medullary thyroid carcinoma or MEN2. Second, pre-existing thyroid disease — defined as levothyroxine replacement, known/suspected autoimmune thyroid disease, or any incompletely characterized nodule — must be characterized to the extent current evidence requires (defined monitoring plan for levothyroxine-treated patients; specialist referral for autoimmune disease or incompletely characterized nodules). Third, the patient should be informed that the strongest available signals at the composite level are modest, that no statistically significant effect has been established for individual sub-conditions including thyroid cancer, and that serial monitoring of thyroid function in the first three months on therapy captures the period of greatest vulnerability for those on levothyroxine. The principle that should govern all such discussions is that thyroid safety is one factor among several — including cardiovascular benefit, weight-loss trajectory, gastrointestinal tolerability, and cost — and that categorical avoidance of GLP-1RA therapy on thyroid grounds alone is supported by neither the molecular nor the clinical epidemiology for the vast majority of patients encountered in routine practice.

Future Research Directions

Four priorities emerge from the present synthesis. Prospective active-comparator registry data with longer follow-up durations (10–20 years) are needed to detect the low-magnitude carcinogenic effect that 3-year cohort follow-up does not adequately exclude (Baxter et al., 2025; Pasternak et al., 2024). A replication of the Boess paired primary C-cell culture experiment with a wider range of human tissue donors and across the full GLP-1RA class would meaningfully clarify whether the species-specific receptor mapping finding established for liraglutide extends to the long-acting and dual/triple-agonist agents (Boess et al., 2013). Mechanistic studies on HPT-axis modulation are needed to determine whether the prospectively observed TSH reductions are centrally mediated, peripherally mediated through altered thyroid hormone clearance, or pharmacokinetically mediated through altered absorption of replacement hormone (Konopka et al., 2024; Sencar et al., 2019; Yu et al., 2023). A targeted pharmacovigilance analysis with formal channeling-bias correction, comparing the agent-level reporting odds ratios from FAERS with newly generated active-comparator cohort data, would clarify whether the FAERS agent ranking represents differential pharmacologic effect or differential notoriety exposure across the marketed agents (D’Arcy et al., 2018; Makunts et al., 2023; Sendor & Stürmer, 2022). The methodological framework of González-González and colleagues for assessing trial trustworthiness should continue to be applied as new primary studies are published (González-González et al., 2019).

Conclusions

Four prospectively defined questions structured this review. Four principal findings emerge.

On thyroid cancer risk, four mutually constraining evidence streams define the current safety profile. Validated receptor autoradiography finds absent GLP-1R expression in human thyroid C-cells (Waser et al., 2014); paired primary C-cell cultures establish that human C-cells lack the rodent calcitonin-release response (Boess et al., 2013); chronic primate toxicology at approximately 500-fold the maximum human dose across 52 weeks produces a null C-cell phenotype (Vahle et al., 2015). RCT meta-analysis shows a composite signal (RR 1.28, 95% CI 1.03–1.60) without sub-domain effects including thyroid cancer (Hu et al., 2022); focused cancer meta-analysis identified MH-OR 1.52 (95% CI 1.01–2.29) carried by fragility index 1 (Silverii et al., 2023). FAERS class-level ROR 21.80 (95% CI 10.25–46.36) is interpretable only as hypothesis-generating given channeling and notoriety bias (D’Arcy et al., 2018; Makunts et al., 2023; Sendor & Stürmer, 2022). The Baxter 2025 multisite active-comparator cohort (98,147 GLP-1RA versus 2,488,303 DPP-4 inhibitor users) yields HR 0.81 (95% CI 0.59–1.12) without dose-response (Baxter et al., 2025), paralleling Pasternak 2024 null at 3.9 years (Pasternak et al., 2024). Regulatory contraindications remain appropriate (Watts et al., 2025).

On levothyroxine-treated patients, class-wide reproducible thyrotropic modulation is supported: oral semaglutide increases levothyroxine exposure by approximately 33% (Hauge et al., 2019, 2021) and produces 0.32 mIU/L TSH reduction at 3 months independent of weight loss (Konopka et al., 2024); exenatide reduces TSH from 2.3 to 1.8 mIU/L at 6 months independent of BMI change (Sencar et al., 2019); tirzepatide suppresses TSH in 5 of 17 patients within 53 days (Yu et al., 2023). Standard 6–8-week post-initiation monitoring is warranted.

On autoimmune thyroid disease, evidence remains dominated by mechanistic plausibility and case-level signals (Jung et al., 2025; Mazokopakis, 2023; Mazza, 2025; Sabudin et al., 2025; Shlomov et al., 2026; Yaribeygi et al., 2024) — informed-consent-level discussion rather than categorical avoidance.

On dual and triple incretin agonists, the evidence base is qualitatively distinct from selective GLP-1RA data. SURMOUNT-3 reports malignancies in 1.7% tirzepatide versus 1.0% placebo participants, with no investigators attributing events as related and no medullary thyroid carcinoma cases (Wadden et al., 2023); FAERS signals arise amid a post-black-box-warning notoriety reporting surge (Humaida et al., 2025; Ou et al., 2024); retatrutide phase 2 thyroid endpoints remain unreported in peer-reviewed literature.

Four future priorities follow: 10–20-year active-comparator registries (Baxter et al., 2025; Pasternak et al., 2024); replication of the Boess paired C-cell culture across the full GLP-1RA class (Boess et al., 2013; Waser et al., 2014); mechanistic HPT-axis modulation studies distinguishing central, peripheral, and absorption-mediated mechanisms (Hauge et al., 2019; Konopka et al., 2024; Sencar et al., 2019; Yu et al., 2023); and channeling-bias-corrected pharmacovigilance re-analysis against FAERS agent-level rankings (D’Arcy et al., 2018; Makunts et al., 2023; Sendor & Stürmer, 2022). New studies should be appraised through the endocrine-trial trustworthiness framework (González-González et al., 2019).

The current regulatory framework — MTC and MEN2 contraindications retained; routine biomarker screening not recommended; standard levothyroxine monitoring in the first 8–12 weeks — is supported by the totality of evidence.

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