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Review

Metabolic Surgery as a Modulator of the Thyroid–Gut Axis: A Narrative Review on Autoimmunity, Function, and Levothyroxine Pharmacokinetics

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Abstract

Background: The interplay between obesity and thyroid dysfunction is complex, characterized by adaptive hyperthyrotropinemia and peripheral hormone resistance. Metabolic and Bariatric surgery (MBS) has emerged not only as a weight-loss (WL) intervention but also as a potent modulator of the thyroid–gut axis. **Methods**: We conducted a narrative review of the literature (2015–2025), synthesizing data from prospective cohorts, meta-analyses, and mechanistic studies to evaluate the impact of MBS on thyroid function, autoimmune dynamics, and drug pharmacokinetics. **Discussion**: Current evidence suggests that MBS promotes a recalibration of the thyroid axis. Post-operative WL is independently associated with a significant reduction in serum thyroid-stimulating hormone (TSH) and free triiodothyronine (fT3) levels, reversing obesity-induced peripheral resistance. Concurrently, the reduction in systemic inflammation (NOD-like receptor protein 3 (NLRP3) inflammasome deactivation) may dampen lymphocytic infiltration, while the amelioration of gut dysbiosis and intestinal permeability is hypothesized to reduce cross-reactivity mechanisms (molecular mimicry), leading to decreased antibody titers in Hashimoto's thyroiditis. However, these benefits are counterbalanced by altered drug absorption mechanisms. While most hypothyroid patients benefit from reduced Levothyroxine (L-T4) requirements due to decreased lean mass, malabsorptive procedures (Roux-en-Y Gastric Bypass, One Anastomosis Gastric Bypass) can precipitate refractory hypothyroidism due to bypassed absorptive surfaces and altered gastric pH. **Conclusions**: MBS offers a dual benefit of functional restoration and modulation of autoimmune markers. However, post-surgical management requires a tailored approach. Clinicians must distinguish between the physiological decline in TSH (adaptive) and iatrogenic malabsorption, advocating for liquid L-T4 formulations in complex malabsorptive phenotypes.

Keywords: bariatric and metabolic surgery; thyroid–gut axis; Hashimoto's thyroiditis; obesity; hypothyroidism

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1. Introduction

The concurrent global rise in obesity and thyroid alterations represents a complex clinical challenge, characterized by a bidirectional relationship that intertwines metabolic

dysregulation with endocrine adaptation. Epidemiological data consistently indicate a higher prevalence of hypothyroidism among individuals with obesity compared to the general population [1]. Furthermore, a positive correlation between Body Mass Index (BMI) and serum Thyroid-Stimulating Hormone (TSH) levels has been observed even in euthyroid subjects, complicating the distinction between pathological thyroid disease and a physiological, adaptive response to adiposity [2].

Historically, elevated TSH in patients with obesity was often misinterpreted solely as a driver of weight gain due to reduced metabolic rate. However, contemporary research suggests that hyperthyrotropinemia in this population is largely a consequence of the obese state rather than its primary cause [3]. Adipose tissue functions as an active endocrine organ, secreting leptin and pro-inflammatory cytokines that stimulate the hypothalamic–pituitary–thyroid (HPT) axis. Concurrently, obesity is associated with a state of inferred peripheral thyroid hormone resistance, necessitating higher TSH levels to maintain homeostasis [4,5]. Moreover, an emerging conceptual framework, often described as the "Thyroid–Gut Axis," postulates that altered intestinal permeability and dysbiosis, which may further trigger autoimmunity via molecular mimicry and nutrient malabsorption [6]. Moreover, chronic low-grade inflammation associated with obesity activates the NOD-like receptor protein 3 (NLRP3) inflammasome, which has been proposed as a potential mediator in the pathogenesis of autoimmune thyroid diseases (AITD) such as Hashimoto's thyroiditis [7].

Metabolic and Bariatric surgery (MBS), including Roux-en-Y Gastric Bypass (RYGB), One Anastomosis Gastric Bypass (OAGB) and Sleeve Gastrectomy (SG), has emerged as the most effective treatment for severe obesity, inducing profound weight loss (WL) and rapid remission of metabolic comorbidities [8–11]. Recent prospective data indicate that MBS does not merely reduce weight but effectively recalibrates the homeostatic set-point of the thyroid axis. Studies have shown significant postoperative reductions in TSH and free Triiodothyronine (fT3), which correlate directly with the percentage of Total WL (%TWL) [2,12]. This functional restoration often translates into a reduced need for thyroid hormone replacement (THR) therapy in hypothyroid patients, with some studies reporting a dose reduction in over 50% of cases [13].

Despite these favorable functional changes, MBS introduces new complexities in the management of patients with established hypothyroidism. While surgery may ameliorate the autoimmune burden by reducing antibody titers [14], the anatomical rearrangement of the gastrointestinal tract can severely alter the pharmacokinetics of oral Levothyroxine (L-T4). The bypass of the proximal jejunum—the primary site of L-T4 absorption—and changes in gastric pH create a potential conflict between the reduced physiological requirement for the hormone (due to WL) and its impaired bioavailability [15]. While predictable pharmacokinetic changes are common, rare cases of severe malabsorption leading to myxedema coma have been reported as a consequence of management failures, underscoring the need for tailored pharmacological strategies [16].

This narrative review synthesizes the most recent evidence (2015–2025) regarding the impact of MBS on the thyroid–gut axis. Specifically, we discuss the morphological and functional regression of thyroid stress post-surgery, the potential for immunological remission in Hashimoto's thyroiditis, and the practical challenges of adjusting thyroid hormone replacement therapy.

2. Materials and Methods

This narrative review synthesizes current evidence regarding the interaction between MBS and thyroid pathophysiology, with a specific focus on autoimmune dynamics and pharmacological management. A comprehensive literature search was conducted using the electronic databases PubMed/MEDLINE, Scopus, and Web of Science up to February 2025. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords, including: 'Bariatric Surgery', 'Metabolic Surgery', "Gastric Bypass", "Sleeve Gastrectomy", "One Anastomosis Gastric Bypass (OAGB)" combined with "Hypothyroidism", "Hashimoto's Thyroiditis", "Thyroid Autoimmunity", "Levothyroxine Absorption", "Thyroid Function Tests", and "TSH". We prioritized the inclusion of original research (prospective and retrospective cohort studies, randomized controlled trials) published primarily between 2015 and 2025 to reflect modern surgical techniques, as well as select case reports describing rare but critical complications. Animal studies and manuscripts not available in English were excluded. However, given the mechanistic nature of the gut–thyroid axis discussion, findings from pre-clinical models are referenced to support translational hypotheses where human data remains associative.

3. Results and Discussion

3.1. Pathophysiology: The Immune-Metabolic Link

The interplay between adipose tissue and the thyroid gland extends far beyond a simple correlation with body weight. It involves a sophisticated network of hormonal crosstalk, inflammatory signaling, and immunological dysregulation [17–20].

3.2. Hormonal Crosstalk: Leptin and TSH Resistance

Adipose tissue secretes leptin, a hormone whose levels are directly proportional to fat mass. Under physiological conditions, leptin stimulates the expression of Thyrotropin-Releasing Hormone (TRH) via the JAK-2/STAT-3 pathway, increasing TSH secretion. In patients with obesity, chronic hyperleptinemia leads to an adaptive elevation of TSH [1].

However, the relationship is bidirectional. Regarding the direct interplay between the thyrotropic axis and adipose tissue, Menendez et al. provided in vitro evidence that TSH exerts a direct stimulatory effect on leptin secretion from human omental adipose tissue via specific TSH Receptor (TSHR) [21]. Under physiological conditions, this creates a feedback loop. However, in the obese state, Nannipieri et al. [18] hypothesized a state of 'adipose tissue TSH resistance' driven by adipocyte hypertrophy and subsequent TSHR downregulation. This receptor reduction impairs the lipolytic and secretagogue effects of TSH, potentially necessitating a compensatory elevation in serum TSH to maintain homeostasis, mimicking the mechanism of insulin resistance.

Leptin is also able to directly influence fT3 levels, as it positively affects the activity of the peripheral deiodinases D1 and D2, promoting the conversion of fT4 into fT3. Following MBS, the reduction in leptin levels removes this stimulatory drive, leading to a rapid decline in TSH and fT3, as shown in Figure 1.

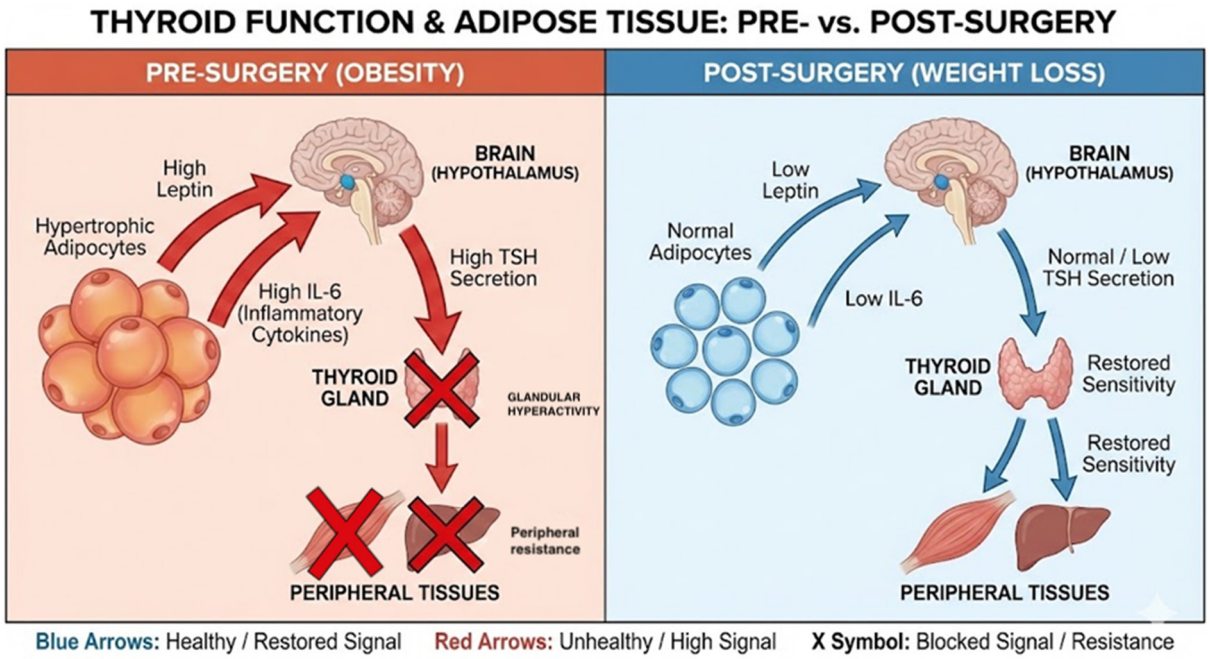

Figure 1. Pathophysiology of the Thyroid–Gut Axis in Obesity. The diagram illustrates the central and peripheral alterations involving the hypothalamus, pituitary, thyroid gland, and target tissues. Note the distinction between peripheral thyroid hormone resistance (reduced sensitivity to T3/T4 in liver and skeletal muscle, often associated with altered deiodinase activity and metabolic syndrome [22]) and the compensatory glandular hyperactivity of the thyroid in response to elevated TSH and leptin stimulation. The figure highlights how obesity-induced inflammation and dysbiosis contribute to resetting the central TSH set-point.

3.3. The Inflammatory Cascade: NLRP3 Inflammasome Activation

Obesity is characterized by chronic low-grade inflammation. Recent evidence identifies the NLRP3 inflammasome as a critical molecular bridge. Excessive saturated fatty acids and oxidized low-density lipoprotein (LDL) in obese patients trigger the NLRP3 inflammasome in macrophages and thyrocytes, releasing IL-1β and IL-18. These cytokines promote lymphocytic infiltration (Hashimoto's thyroiditis) and impair the expression of the sodium/iodide symporter (NIS) [5]. MBS significantly reduces systemic inflammatory markers (IL-6, TNF-α), likely deactivating the NLRP3 inflammasome and potentially contributing to the post-operative functional recovery.

3.4. The Thyroid–Gut Axis: Dysbiosis and Autoimmunity

The bidirectional communication between the gastrointestinal tract and the thyroid gland, often conceptualized as the "Thyroid–Gut Axis," has emerged as a critical environmental determinant in the pathogenesis of autoimmune thyroid diseases (AITD). Patients affected by obesity often exhibit a profound alteration of this axis, driven by two interconnected mechanisms: the impairment of the intestinal barrier and the loss of immune tolerance due to dysbiosis [1,23].

First, the chronic low-grade inflammation associated with obesity is hypothesized to downregulate the expression of tight junction proteins, specifically Zonulin and Occludin, leading to increased intestinal permeability ("Leaky Gut") [23]. This barrier disruption facilitates the translocation of bacterial components, such as Lipopolysaccharide (LPS), from the lumen into the systemic circulation. Recent evidence suggests that this "metabolic endotoxemia" may activate Toll-Like Receptor 4 (TLR4) on thyrocytes and immune cells, promoting a pro-inflammatory milieu that exacerbates autoimmune responses [24,25].

Second, distinct dysbiotic patterns have been linked to thyroid autoimmunity. Compared to healthy controls, patients with Hashimoto's thyroiditis frequently display a reduction in beneficial, anti-inflammatory genera such as *Lactobacillaceae* and *Bifidobacterium*, alongside an overgrowth of potentially pathogenic groups like *Bacteroides* and *Enterobacteriaceae* [24,26]. This imbalance is thought to trigger autoimmunity through "Molecular Mimicry": due to structural sequence homologies between specific bacterial antigens and thyroid autoantigens (Thyroid peroxidase [TPO] and Thyroglobulin [Tg]), the immune system may generate cross-reactive antibodies that sustain the attack on the thyroid gland [25].

Furthermore, this dysbiotic state compromises the intestinal absorption of essential micronutrients required for thyroid hormone synthesis and conversion, such as Selenium, Zinc, and Iodine [4]. Consequently, metabolic surgery, by drastically modifying the gastric pH and inducing weight-loss-dependent shifts in the microbiome, has the potential to modulate these pathogenic pathways. While clinical improvement is frequently observed, direct causal evidence linking post-surgical microbiota shifts to immunological remission in humans remains to be definitively established [15,16].

3.5. Clinical Outcomes: From Functional Restoration to Morphological Regression

The impact of MBS facilitates a profound functional and structural remodeling of the thyroid gland, with changes that involve thyroid function tests, gland morphology, autoimmunity, and levothyroxine requirements [27–29].

3.6. Functional Recalibration: The Decline of TSH and fT3

Post-operative data consistently demonstrate a downward recalibration of the TSH set-point in patients affected by obesity. In the prospective study by Misra et al. (2025), which included 156 hypothyroid patients undergoing different bariatric procedures, mean serum TSH levels decreased from 7.78 ± 11.11 to 2.61 ± 1.62 mIU/L at 1 year, with a parallel significant reduction in thyroid replacement therapy dosage [4]. These findings are in line with the retrospective analysis by Tian et al. (2024), who observed significant decreases in TSH, fT3, and fT4 levels after MBS [2]. The reduction in fT3 is generally interpreted as a consequence of decreased metabolic demand and a lower leptin-mediated stimulation of deiodinase activity following WL [2].

3.7. The Dose–Response Relationship and Metabolic Prediction

The extent of recovery depends on WL. Tian et al. identified %TWL as an independent predictor of TSH reduction, reinforcing the link between the magnitude of WL and thyroid axis normalisation [2]. Conversely, preoperative TSH levels may themselves predict metabolic benefit: in the cohort studied by Bian et al. (2021), patients with higher baseline TSH experienced more pronounced improvements in adipose tissue insulin resistance (Adipo-IR) post-surgery [30].

3.8. Morphological Regression

Obesity is a recognised risk factor for goiter. de Sousa et al. (2023) provided prospective evidence that MBS was associated with a significant reduction in thyroid volume (approximately -1.5 cm^3) which correlated with improvements in insulin resistance and inflammatory markers such as IL-6 [31]. Although statistically significant, this volumetric reduction is often clinically marginal and should be interpreted with caution regarding its direct impact on patient management.

3.9. Reduction in Autoimmunity

Beyond functional and structural changes, MBS may also modulate thyroid autoimmunity. Xia et al. (2019) documented a significant post-operative decline in TPOAb and TgAb

serum levels following surgery, suggesting that the surgical reduction in adipose tissue and systemic inflammation can dampen the autoimmune drive in Hashimoto's thyroiditis, representing an immunological modulation rather than definitive disease remission [14].

3.10. Pharmacological Challenges: The Absorption Dilemma

While MBS generally improves thyroid function, it introduces complexity to the management of hypothyroidism [10,32–37]. L-T4 is absorbed mainly in the jejunum and ileum, and adequate gastric acidity is required for tablet dissolution and subsequent intestinal uptake. MBS may alter this process by reducing gastric acid (impairing dissolution) and, in bypass procedures, excluding the primary absorptive surface, as shown in Figure 2. Clinicians should define malabsorption as 'refractory' only after ruling out non-adherence and attempting dose titration with standard formulations. A switch to liquid L-T4 is recommended as a second-line strategy for patients with persistent TSH elevation despite adequate tablet dosing.

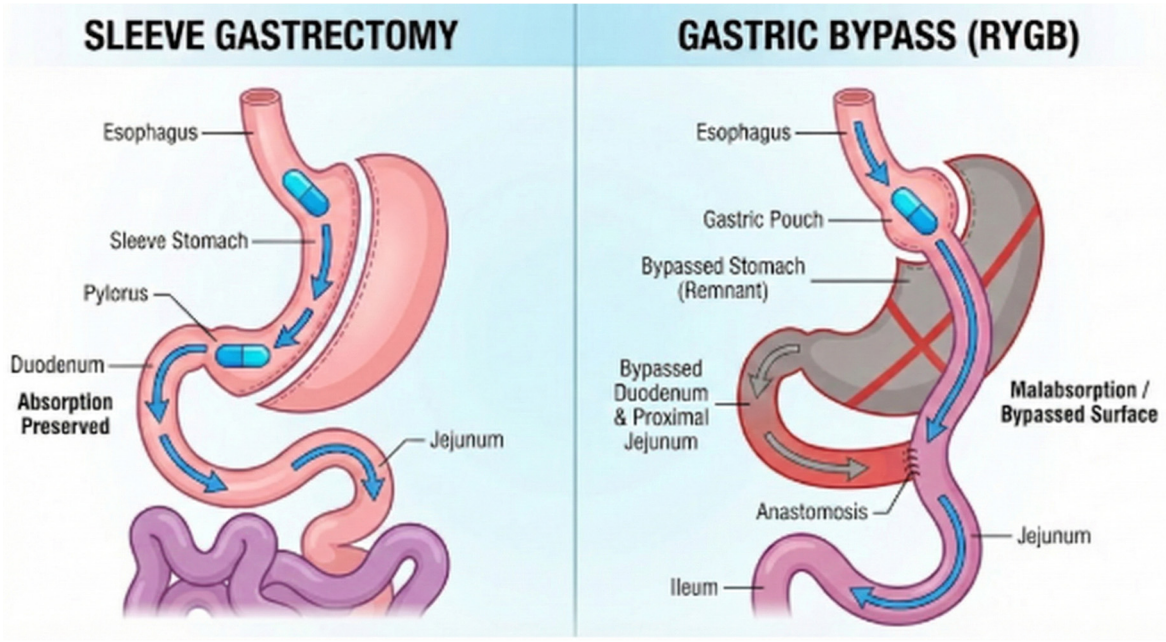

Figure 2. Pharmacokinetic Challenges by Procedure Type. (**Left**) Sleeve Gastrectomy: The stomach volume is reduced, potentially altering pH, but the transit through the duodenum (primary absorption site) is preserved. (**Right**) Bypass Procedures (RYGB): The stomach pouch is small, and the proximal intestine is bypassed (red area), reducing the mucosal surface available for L-T4 tablet dissolution and absorption. Note: The One Anastomosis Gastric Bypass (OAGB) shares a similar malabsorptive mechanism by excluding the proximal jejunum, albeit with a single loop reconstruction (not depicted).

3.11. Surgical Technique Matters: SG vs. RYGB/OAGB

- SG: Intestinal continuity is preserved. The "WL effect" (reduced stomach dimension) typically dominates. Demirpolat et al. (2024) found that >50% of patients discontinued therapy post-SG [13,36,38]. In a previous study, Rudnicki et al. demonstrated that both SG and RYGB improved thyroid function even if no procedure was found to be superior. Moreover, no correlation was found between %EWL and TSH reduction, suggesting that the effect of MBS on the improvement of thyroid functions is mediated probably by hormonal mechanisms rather than WL alone [32]. According to those studies, Yang et al. also confirmed in their cohort that TSH levels decreased after SG, with FT3 and FT4 being steady. without correlation with %EWL or %TWL [38].

- Gastric Bypass (RYGB/OAGB): The risk of malabsorption is higher due to bypass mechanism. Barzin et al. (2024) noted that patients undergoing OAGB experienced greater fluctuations in L-T4 requirements compared to SG [27,39,40].

3.12. Managing Refractory Malabsorption

In rare cases, anatomical changes lead to refractory hypothyroidism. Gruneisen et al. (2025) reported severe hypothyroidism post-SG confirmed by a T4 absorption test [15], and Buoso et al. (2024) documented myxedema coma in a bypass patient switching to tablets [16]. These cases underscore the need for liquid formulations that bypass the dissolution phase.

3.13. Visual Resumè of Literature Analyzed

To provide a comprehensive overview of the analyzed literature, Table 1 summarizes the key findings of the included studies, detailing the hormonal variations and clinical outcomes observed.

Table 1. Summary of key studies evaluating thyroid outcomes after bariatric surgery.

Study Author (Year)	Study Design/N	Intervention	Impact on Thyroid Function	Impact on Medication/Pharmacokinetics
Tian et al. (2024) [2]	Retrospective/256	LSG, RYGB	TSH, fT3, and fT4 decreased significantly. %TWL is an independent predictor of TSH decline.	N/A (Euthyroid cohort).
Misra et al. (2025) [4]	Prospective/314	LSG, RYGB, OAGB	Significant TSH reduction at 1 year ($p = 0.018$). Negative correlation between TSH and %TWL.	Thyroid replacement therapy (TRT) dosage significantly reduced ($p < 0.001$).
Demirpolat et al. (2024) [13]	Retrospective/51	LSG	Significant TSH reduction.	50.9% of patients ceased levothyroxine; 41% required dose reduction.
Xia et al. (2019) [14]	Retrospective/101	LSG, RYGB	Serum TPOAb and TgAb titers decreased significantly post-surgery.	Improved autoimmunity linked to reduced systemic inflammation.
de Sousa et al. (2023) [31]	Prospective/70	LSG, RYGB	Thyroid Volume reduced by 1.5 cm^3 post-surgery.	Morphological regression correlated with improved insulin resistance (HOMA-IR).
Barzin et al. (2024) [40]	Cohort/1030	LSG vs. OAGB	TSH decreased in both groups.	OAGB patients experienced greater fluctuations and higher dose adjustments than LSG.

Note: This table is an original compilation by the authors, based on data extracted from the cited references.

3.14. Practical Recommendations for Clinicians

Based on expert opinion, we propose the following clinical approach (illustrated in Figure 3):

- Preoperative Assessment: Screen all candidates for TSH and TPOAb. Differentiate "obesity-related hyperthyrotropinemia" (usually mild, TSH < 10, normal fT4, often antibody-negative) from true Hashimoto's.
- Postoperative Monitoring: Check TSH at 6 weeks post-surgery.
  - If TSH is suppressed: Reduce L-T4 dose (anticipated effect of WL).
  - If TSH is elevated: Verify compliance. If confirmed, suspect malabsorption.
- Therapeutic Strategy: For patients with malabsorption (common in OAGB/RYGB), switch from tablets to liquid L-T4 or soft-gel capsules. Ensure L-T4 is taken 4 h apart from calcium/iron supplements.

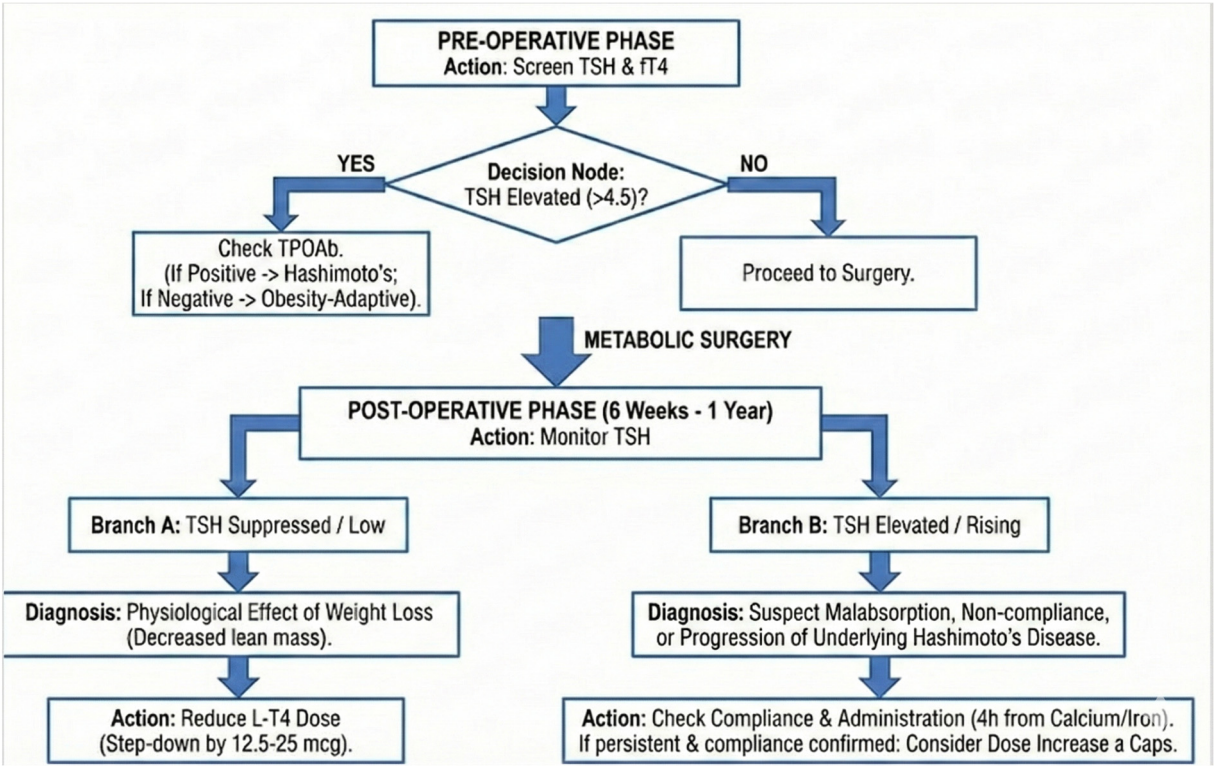

Figure 3. Proposed clinical algorithm for thyroid hormone management after Metabolic Bariatric Surgery (MBS). Based on expert opinion, the flowchart guides dose adjustments according to postoperative TSH trends. **Branch A** addresses the physiological reduction in TSH levels driven by weight loss and decreased lean body mass, which typically necessitates a dose reduction. **Branch B** outlines the management of persistent or rising TSH (refractory hypothyroidism): after ruling out non-adherence (pseudo-malabsorption), the clinician must differentiate between true iatrogenic malabsorption and the natural progression of Hashimoto's thyroiditis (loss of functional reserve). In these refractory cases, switching to liquid or soft-gel L-T4 formulations is recommended as a second-line strategy.

3.15. Future Perspectives

While the interplay between MBS and the "thyroid–gut axis" is becoming clearer, significant knowledge gaps remain. Future research should prioritize longitudinal studies integrating metagenomic sequencing to definitively establish whether post-surgical microbiome shifts are the cause of autoimmunity remission or merely a bystander effect. Furthermore, randomized controlled trials comparing tablet versus liquid L-T4 formula-

tions immediately post-surgery are needed to define the optimal prophylactic strategy. Finally, long-term data are required to determine if the 'recalibration' of the TSH set-point confers cardiovascular or metabolic protection, or if it warrants new reference ranges specific to the post-bariatric population.

4. Conclusions

MBS represents a pivotal event in the life of a patient with obesity, acting as a potent modulator of the thyroid axis. The evidence highlighted in this discussion reveals a dual effect: a beneficial physiological restoration and a potential pharmacological challenge. From a functional perspective, the WL induced by surgery effectively recalibrates the TSH drive, reducing TSH, fT3, and thyroid volume, and potentially modulating autoimmune markers. However, these benefits must be balanced against altered pharmacokinetics. While the majority of patients will require lower doses of L-T4, a subset—particularly those undergoing malabsorptive procedures—may face refractory malabsorption in cases where a supplement is needed. In the era of precision MBS, the endocrinologist's role must evolve from simple monitoring to proactive management, with a lower threshold for adopting liquid formulations in high-risk phenotypes. Finally, it must be emphasized that this narrative review serves as an interpretative and exploratory synthesis of current hypotheses rather than a source of definitive mechanistic conclusions.

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Abbreviations

The following abbreviations are used in this manuscript:

ADIPO-IR	Adipose tissue insulin resistance
AITD	Autoimmune thyroid diseases
BMI	Body Mass Index
EWL	Excess Weight Loss
fT3	Free Triiodothyronine
fT4	Free Thyroxine
HPT	Hypothalamic–Pituitary–Thyroid
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-18	Interleukin-18
LDL	Low-Density Lipoprotein

L-T4	Levothyroxine
MBS	Metabolic and Bariatric Surgery
MeSH	Medical Subject Headings
NIS	Sodium/Iodide Symporter
NLRP3	NOD-like Receptor Protein 3
OAGB	One Anastomosis Gastric Bypass
RYGB	Roux-en-Y Gastric Bypass
SG	Sleeve Gastrectomy
Tg	Thyroglobulin
TgAb	Thyroglobulin Antibodies
THR	Thyroid Hormone Replacement
TNF-α	Tumor Necrosis Factor-alpha
TPO	Thyroid Peroxidase
TPOAb	Thyroid Peroxidase Antibodies
TRH	Thyrotropin-Releasing Hormone
TSH	Thyroid-Stimulating Hormone
TSHR	TSH Receptor
TWL	Total Weight Loss
WL	Weight Loss

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