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A Narrative Review On Effect Of Checkpoint Inhibitors On Thyroid Function

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ABSTRACT:

Immune checkpoint inhibitors (ICIs), including agents targeting PD-1, PD-L1, and CTLA-4, have revolutionized cancer therapy by enhancing antitumor immunity. However, their use is frequently complicated by immune-related adverse events (irAEs), with thyroid dysfunction being the most common endocrine manifestation. Understanding the incidence, mechanisms, and clinical implications of ICI-induced thyroid disorders is essential for optimizing patient care. Studies were analyzed for incidence rates, mechanistic insights, clinical features, and therapeutic recommendations.

Thyroid dysfunction occurs in 7–20% of patients receiving ICIs, with higher incidence in combination therapy. The predominant pattern is destructive thyroiditis, leading to transient thyrotoxicosis followed by permanent hypothyroidism. Mechanistically, CD8+ T-cell infiltration, cytokine release (IL-2, IFN-γ), and autoantibody involvement contribute to thyroid injury. Clinical presentations range from asymptomatic laboratory abnormalities to overt thyrotoxicosis or hypothyroidism requiring lifelong levothyroxine. Routine monitoring of thyroid function every 4–6 weeks is recommended. Most cases can be managed without discontinuing ICIs, though endocrinology referral is warranted for severe or atypical presentations.

ICIs significantly improve cancer outcomes but carry a substantial risk of thyroid dysfunction. Early recognition, structured monitoring, and timely intervention are critical. Pharmacists play a significant role in patient education, adherence to thyroid hormone replacement, and pharmacovigilance. Future research should focus on predictive biomarkers and personalized monitoring strategies to balance oncologic efficacy with endocrine safety.

Keywords: Immune checkpoint inhibitors, thyroid dysfunction, hypothyroidism, thyrotoxicosis, immune-related adverse events.

INTRODUCTION:

The advent of immune checkpoint inhibitors (ICIs) has marked a paradigm shift in oncology, offering durable responses and improved survival in a wide range of malignancies, including melanoma, non-small cell lung cancer, renal cell carcinoma, and head and neck cancers. By targeting inhibitory pathways such as programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), ICIs restore and enhance T-cell mediated antitumor immunity. This therapeutic breakthrough, however, comes at the cost of immune-related adverse events (irAEs), which reflect the unintended activation of the immune system against normal tissues.

Among the spectrum of irAEs, endocrine toxicities are particularly significant due to their potential to cause long-term morbidity. Thyroid dysfunction has emerged as the most common endocrine irAE associated with ICIs, with reported incidence ranging from 7% to 20% depending on the agent and treatment regimen. The clinical spectrum includes transient thyrotoxicosis, destructive thyroiditis, hypothyroidism requiring lifelong replacement therapy, and, less commonly, Graves' disease. These manifestations can occur early during treatment or months after therapy initiation, underscoring the need for vigilant monitoring.

The pathophysiology of ICI-induced thyroid dysfunction is multifactorial. Enhanced T-cell activation leads to infiltration of thyroid tissue, accompanied by cytokine release and, in some cases, the presence of thyroid autoantibodies. Genetic predisposition, such as HLA polymorphisms, may further increase susceptibility. Unlike classical autoimmune thyroid disease, ICI-induced thyroiditis often follows a biphasic course, beginning with thyrotoxicosis and progressing to hypothyroidism, reflecting irreversible follicular cell destruction.

Clinically, thyroid dysfunction may present with nonspecific symptoms such as fatigue, weight changes, palpitations, or mood disturbances, which can overlap with cancer-related symptoms or treatment side effects. This overlap poses diagnostic challenges, making routine biochemical monitoring essential. Current guidelines recommend baseline thyroid function testing prior to ICI initiation, followed by periodic assessments every 4–6 weeks during therapy. Early detection allows timely intervention, minimizing morbidity and ensuring continuity of cancer treatment.

From a therapeutic perspective, most cases of thyroid dysfunction can be managed without discontinuing ICIs. Symptomatic thyrotoxicosis is treated with beta-blockers, while hypothyroidism requires levothyroxine replacement. Severe or atypical cases warrant endocrinology referral. Importantly, the occurrence of thyroid irAEs does not typically compromise oncologic outcomes and may, in some studies, correlate with improved antitumor efficacy, suggesting a complex interplay between immune activation and therapeutic benefit.

Pharmacists and other healthcare professionals play a pivotal role in this context. Their responsibilities include patient education, monitoring adherence to thyroid hormone replacement, identifying drug interactions, and contributing to pharmacovigilance efforts. As ICIs become increasingly integrated into cancer care, multidisciplinary collaboration is essential to balance oncologic efficacy with endocrine safety.

This narrative review aims to synthesize current evidence on the incidence, mechanisms, clinical presentation, and management of thyroid dysfunction induced by ICIs. By highlighting both clinical and pharmacological perspectives, the review underscores the importance of structured monitoring and multidisciplinary care, while identifying gaps for future research, particularly in predictive biomarkers and personalized management strategies.

EPIDEMIOLOGY:

Thyroid dysfunction is the most frequently reported endocrine immune-related adverse event (irAE) associated with immune checkpoint inhibitors (ICIs), with an overall incidence ranging between 7% and 20% depending on the agent and treatment regimen. Hypothyroidism is the predominant manifestation, occurring in approximately 6–15% of patients treated with PD-1 inhibitors such as nivolumab or pembrolizumab, while transient thyrotoxicosis is observed in 3–8% of cases. PD-L1 inhibitors, including atezolizumab and durvalumab, are associated with slightly lower rates of thyroid dysfunction, whereas CTLA-4 inhibitors like ipilimumab rarely cause thyroid disorders when used as monotherapy. Importantly, combination therapy, particularly nivolumab plus ipilimumab, carries the highest risk, with thyroid dysfunction reported in up to 20–25% of patients and often presenting earlier in the treatment course. The median onset of thyroid dysfunction is typically 6–12 weeks after initiation of therapy, although delayed cases have been documented months after discontinuation, underscoring the need for long-term surveillance. Several risk factors have been identified, including pre-existing thyroid

autoantibodies, which significantly increase the likelihood of developing hypothyroidism, and genetic susceptibility such as HLA-DR polymorphisms.

Clinical outcomes vary, with most patients progressing to permanent hypothyroidism requiring lifelong levothyroxine replacement, while thyrotoxicosis is generally self-limiting and managed symptomatically. Rare presentations such as Graves' disease or mixed thyroiditis have also been reported. Despite the high incidence, surveillance remains inconsistent, with nearly half of patients lacking post-treatment thyroid monitoring, leading to under-recognition of late-onset dysfunction. Current guidelines recommend baseline thyroid function testing followed by routine monitoring every 4–6 weeks during therapy, highlighting the importance of structured follow-up to ensure timely detection and management.

Table 1. Incidence of Thyroid Dysfunction by Checkpoint Inhibitor Class

Checkpoint Inhibitor	Common Agents	Incidence of Hypothyroidism	Incidence of Thyrotoxicosis	Notes
PD-1 inhibitors	Nivolumab, Pembrolizumab	6–15%	3–8%	Most frequent thyroid irAEs
PD-L1 inhibitors	Atezolizumab, Durvalumab	4–10%	2–5%	Slightly lower incidence
CTLA-4 inhibitors	Ipilimumab	2–5%	<2%	Rare as monotherapy
Combination therapy	Nivolumab + Ipilimumab	20–25%	10–15%	Highest risk

PATHOPHYSIOLOGY:

The pathophysiology of thyroid dysfunction induced by immune checkpoint inhibitors (ICIs) reflects the fundamental mechanism of these agents: the restoration of T-cell activity through blockade of inhibitory pathways such as PD-1/PD-L1 and CTLA-4. While this enhances antitumor immunity, it simultaneously disrupts immune tolerance, allowing autoreactive T-cells to target normal tissues, including the thyroid gland.

Immune Activation and Thyroid Infiltration:

ICIs remove inhibitory signals that normally restrain T-cell activation. This results in heightened cytotoxic CD8+ T-cell activity and infiltration of thyroid tissue. Histopathological studies have demonstrated dense lymphocytic infiltration of thyroid follicles, consistent with destructive thyroiditis. The immune attack leads to rapid follicular cell destruction, releasing preformed thyroid hormones into circulation and causing transient thyrotoxicosis. As follicular reserves are depleted, permanent hypothyroidism ensues.

Cytokine-Mediated Injury:

Activated T-cells release pro-inflammatory cytokines such as interleukin-2 (IL-2), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α). These cytokines amplify local inflammation, recruit additional immune cells, and accelerate thyroid tissue damage. The cytokine milieu resembles that seen in autoimmune thyroiditis but is often more aggressive due to the systemic immune activation induced by ICIs.

Role of Autoantibodies:

Thyroid autoantibodies, particularly anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg), are frequently detected in patients who develop ICI-induced thyroid dysfunction. Pre-existing antibody positivity is a strong predictor of hypothyroidism, with studies showing up to 40–50% of antibody-positive patients progressing to overt disease. While autoantibodies may not be the primary driver, they likely contribute to the autoimmune cascade and perpetuate thyroid injury.

Genetic Susceptibility:

Genetic predisposition plays a role, with certain HLA-DR polymorphisms associated with increased risk of thyroid irAEs. These genetic factors may influence antigen presentation and the threshold for immune activation, thereby modulating susceptibility to thyroid autoimmunity under ICI therapy.

Distinctive Clinical Course:

Unlike classical autoimmune thyroid disease, ICI-induced thyroiditis often follows a biphasic course. The initial phase is characterized by thyrotoxicosis due to hormone release from damaged follicles, followed by a hypothyroid phase as glandular destruction becomes irreversible. This pattern underscores the destructive nature of ICI-induced thyroiditis, distinguishing it from conditions such as Graves' disease, where hyperthyroidism is sustained by autoantibody stimulation rather than tissue destruction.

Potential Links to Antitumor Efficacy:

Interestingly, the occurrence of thyroid irAEs has been correlated with improved oncologic outcomes in some studies. This suggests that robust immune activation sufficient to cause thyroid autoimmunity may also reflect enhanced antitumor immunity, highlighting the complex interplay between therapeutic benefit and adverse effects.

Key Points

- ICIs disrupt immune tolerance, enabling autoreactive T-cell infiltration of thyroid tissue.
- Cytokine release (IL-2, IFN-γ, TNF-α) amplifies thyroid destruction.
- Autoantibody positivity increases risk but is not the sole driver.
- Genetic predisposition (HLA polymorphisms) modulates susceptibility.
- The biphasic course (thyrotoxicosis → hypothyroidism) is characteristic of ICI-induced thyroiditis.
- Thyroid irAEs may paradoxically correlate with improved cancer outcomes.

Conceptual Flow Diagram:

Checkpoint Inhibitor Therapy
↓
Immune Checkpoint Blockade (PD-1/PD-L1, CTLA-4)
↓
Enhanced T-cell Activation
↓
CD8+ T-cell Infiltration into Thyroid
↓
Cytokine Release (IL-2, IFN-γ, TNF-α)
↓
Thyroid Follicular Cell Destruction
↓
Transient Thyrotoxicosis → **Hypothyroidism**

CLINICAL CHARACTERIZATION:

Thyroid dysfunction induced by immune checkpoint inhibitors (ICIs) presents with a wide clinical spectrum, ranging from asymptomatic laboratory abnormalities to overt endocrine disease requiring lifelong treatment. The most common presentations include transient thyrotoxicosis, destructive thyroiditis, and hypothyroidism, while rare cases of Graves' disease and mixed thyroiditis have also been reported. The clinical course is often biphasic, beginning with thyrotoxicosis due to follicular cell destruction and progressing to hypothyroidism as glandular reserves are depleted.

Thyrotoxicosis:

Patients may present with palpitations, weight loss, tremors, heat intolerance, and anxiety. In most cases, thyrotoxicosis is mild and self-limiting, lasting 2–6 weeks. Laboratory findings typically reveal suppressed thyroid-stimulating hormone (TSH) with elevated free thyroxine (fT4) and triiodothyronine (T3). Unlike Graves' disease, thyrotoxicosis in ICI-induced thyroiditis is not sustained by thyroid-stimulating antibodies but results from destructive release of preformed hormones. Imaging, when performed, shows a hypoechoic, heterogeneous thyroid consistent with inflammation.

Hypothyroidism:

This is the most frequent outcome, occurring in up to 15% of patients treated with PD-1 inhibitors. Symptoms include fatigue, weight gain, cold intolerance, constipation, and depression, which may overlap with cancer-related symptoms, complicating diagnosis. Laboratory findings show elevated TSH with low fT4. Hypothyroidism is often permanent, requiring lifelong levothyroxine replacement. The transition from thyrotoxicosis to hypothyroidism is characteristic of ICI-induced thyroiditis.

Graves' Disease and Rare Presentations:

Although uncommon, Graves' disease has been reported in patients receiving ICIs, characterized by persistent hyperthyroidism, diffuse goiter, and ophthalmopathy. These cases require antithyroid drugs and specialist management. Mixed thyroiditis, with alternating phases of hyper- and hypothyroidism, has also been described, though rare.

Subclinical Thyroid Dysfunction:

A significant proportion of patients remain asymptomatic, with abnormalities detected only through routine monitoring. Subclinical hypothyroidism, defined by elevated TSH with normal fT4, is particularly common and may progress to overt disease if untreated.

Diagnostic Challenges:

Clinical characterization is complicated by the nonspecific nature of symptoms, which often overlap with cancer-related fatigue, weight changes, or treatment side effects. Routine biochemical monitoring is therefore essential for timely detection. Baseline thyroid function tests prior to ICI initiation, followed by assessments every 4–6 weeks, are recommended. Autoantibody testing (anti-TPO, anti-Tg) may help identify patients at higher risk, while thyroid ultrasound can support diagnosis in atypical cases.

Clinical Course and Prognosis:

Most patients tolerate thyroid dysfunction without requiring discontinuation of ICIs. In fact, some studies suggest that the occurrence of thyroid irAEs may correlate with improved oncologic outcomes, reflecting robust immune activation. With appropriate management, endocrine complications rarely compromise cancer therapy, but they do necessitate long-term follow-up and patient education.

FUNCTIONAL CHANGES IN THYROID FUNCTION WITH CHECKPOINT INHIBITORS

Immune checkpoint inhibitors profoundly alter thyroid physiology by disrupting immune tolerance and triggering autoimmune-mediated injury. The functional changes observed in patients receiving ICIs reflect both direct immune-mediated destruction of thyroid tissue and secondary hormonal imbalances.

1. Transient Thyrotoxicosis:

- **Mechanism:** Rapid destruction of thyroid follicular cells releases preformed thyroid hormones into circulation.
- **Functional impact:** Elevated basal metabolic rate, weight loss, tachycardia, heat intolerance, and anxiety.
- **Clinical course:** Typically self-limiting, lasting 2–6 weeks, and often progresses to hypothyroidism.

2. Hypothyroidism (Hypometabolic Phase):

- **Mechanism:** Irreversible loss of thyroid follicular cells leads to reduced hormone synthesis.
- **Functional impact:** Fatigue, weight gain, cold intolerance, bradycardia, constipation, and cognitive slowing.
- **Clinical course:** Permanent in most cases, requiring lifelong levothyroxine replacement.

3. Subclinical Thyroid Dysfunction:

- **Mechanism:** Mild immune-mediated injury without overt symptoms.
- **Functional impact:** Elevated TSH with normal free T4; may contribute to subtle fatigue and mood changes.
- **Clinical course:** Can progress to overt hypothyroidism if untreated.

4. Rare Functional Changes (Graves' Disease, Mixed Thyroiditis):

- **Graves' disease:** Persistent hyperthyroidism due to thyroid-stimulating antibodies, leading to sustained metabolic acceleration and ophthalmopathy.
- **Mixed thyroiditis:** Alternating phases of hyper- and hypothyroidism, complicating functional stability and requiring close monitoring.

5. Systemic Consequences in Cancer Patients:

- **Metabolic stress:** Thyrotoxicosis exacerbates cancer-related cachexia, while hypothyroidism worsens fatigue and reduces treatment tolerance.
- **Cardiovascular effects:** Hyperthyroidism increases arrhythmia risk, while hypothyroidism contributes to dyslipidemia and reduced cardiac output.
- **Neurocognitive changes:** Both phases impair mood, cognition, and quality of life, affecting adherence to cancer therapy.
- **Oncologic correlation:** Interestingly, thyroid irAEs have been linked to improved cancer outcomes, suggesting that robust immune activation sufficient to cause thyroid dysfunction may also enhance antitumor efficacy.

MANAGEMENT STRATEGIES AND THERAPEUTIC APPROACHES:

The management of thyroid dysfunction induced by immune checkpoint inhibitors (ICIs) requires a balance between maintaining oncologic efficacy and ensuring endocrine safety. Most cases can be managed effectively without discontinuing ICIs, provided that thyroid function is monitored regularly and appropriate interventions are initiated promptly.

1. Screening and Monitoring

- **Baseline testing:** Thyroid-stimulating hormone (TSH) and free thyroxine (fT4) should be measured prior to initiating ICI therapy.
- **Routine monitoring:** Repeat thyroid function tests every 4–6 weeks during treatment and periodically after discontinuation, as late-onset dysfunction is common.
- **Risk stratification:** Patients with pre-existing thyroid autoantibodies (anti-TPO, anti-Tg) should be monitored more closely, given their higher risk of developing hypothyroidism.

2. Management of Thyrotoxicosis

- **Symptomatic treatment:** Beta-blockers (e.g., propranolol) are used to control palpitations, tremors, and tachycardia.
- **Antithyroid drugs:** Rarely required, as thyrotoxicosis is usually transient and destructive rather than antibody-driven.

- **Monitoring progression:** Regular thyroid function tests to detect transition into hypothyroidism.

3. Management of Hypothyroidism

- **Levothyroxine replacement:** Initiated when TSH is elevated with low fT4 or in symptomatic patients.
- **Dose adjustment:** Titrated based on TSH levels, with follow-up testing every 6–8 weeks until stable.
- **Long-term therapy:** Most cases require lifelong replacement, as thyroid destruction is irreversible.

4. Rare Presentations (Graves' Disease, Mixed Thyroiditis)

- **Graves' disease:** Managed with antithyroid drugs (methimazole, carbimazole) and endocrinology referral.
- **Mixed thyroiditis:** Requires individualized management with close biochemical monitoring due to alternating phases of hyper- and hypothyroidism.

5. Continuation of ICI Therapy

- In most cases, thyroid dysfunction does not necessitate discontinuation of ICIs.
- Severe or atypical cases may require temporary suspension, but therapy is usually resumed once endocrine status is stabilized.
- Multidisciplinary coordination between oncologists and endocrinologists is essential.

6. Pharmacist's Role in Management

- **Patient education:** Counseling patients on recognizing symptoms such as fatigue, palpitations, or weight changes.
- **Medication adherence:** Ensuring proper use of levothyroxine, including guidance on timing and avoidance of drug-food interactions (e.g., calcium or iron supplements).
- **Pharmacovigilance:** Reporting thyroid irAEs to improve safety databases and guide future practice.

7. Long-Term Follow-Up

- **Survivorship care:** Thyroid dysfunction contributes to chronic morbidity in cancer survivors, necessitating ongoing endocrine follow-up.
- **Quality of life:** Addressing fatigue, mood disturbances, and metabolic changes improves patient well-being and treatment adherence.
- **Research opportunities:** Identifying predictive biomarkers and developing personalized monitoring strategies remain priorities for future studies.

Table 2. Clinical Presentation and Management of ICI-Induced Thyroid Dysfunction

Presentation	Typical Onset	Symptoms	Management	Continuation of ICI
Transient thyrotoxicosis	4–8 weeks	Palpitations, weight loss, tremors	Beta-blockers, supportive care	Usually continued
Hypothyroidism	6–12 weeks or later	Fatigue, weight gain, cold intolerance	Levothyroxine replacement	Continued
Graves' disease	Rare	Ophthalmopathy, diffuse goiter	Antithyroid drugs, endocrinology referral	Case-dependent
Subclinical thyroiditis	Any time	Asymptomatic, abnormal labs	Monitoring only	Continued

Monitoring Algorithm for Thyroid Function in ICI Therapy

Start ICI Therapy
↓
Baseline TSH, T_3, T_4
↓
Routine Monitoring Every 4–6 Weeks
↓
Normal Labs Report → Continue Monitoring
↓
Abnormal Labs Report Detected
↓
If Thyrotoxicosis → Symptomatic treatment (beta-blockers)
If Hypothyroidism → Start Levothyroxine
↓
Continue ICI Therapy (unless severe)
↓
Endocrinology Referral for Complex Cases

CONCLUSION:

Immune checkpoint inhibitors (ICIs) have transformed the landscape of oncology by offering durable responses across a wide spectrum of malignancies. However, their therapeutic success is accompanied by immune-related adverse events, with thyroid dysfunction emerging as the most common endocrine complication. The clinical spectrum ranges from transient thyrotoxicosis to permanent hypothyroidism, with rare presentations such as Graves' disease and mixed thyroiditis. These functional changes are driven by immune-mediated follicular cell destruction, cytokine release, and, in some cases, autoantibody involvement, reflecting a complex interplay between immune activation and endocrine regulation.

From a clinical perspective, thyroid dysfunction in cancer patients has profound implications. It exacerbates fatigue, metabolic imbalance, cardiovascular strain, and neurocognitive impairment, all of which can compromise treatment tolerance and quality of life. Yet, paradoxically, the occurrence of thyroid immune-related adverse events has been associated with improved oncologic outcomes, suggesting that robust immune activation sufficient to cause thyroid autoimmunity may also enhance antitumor efficacy. This duality underscores the importance of vigilant monitoring and balanced management strategies.

Routine thyroid function testing before and during ICI therapy is essential for early detection, while structured follow-up after treatment ensures recognition of late-onset dysfunction. Most cases can be managed effectively with symptomatic therapy for thyrotoxicosis and lifelong levothyroxine replacement for hypothyroidism, without discontinuing ICIs. Multidisciplinary collaboration—particularly involving oncologists, endocrinologists, and pharmacists—is critical to optimize patient care. Pharmacists play a pivotal role in patient education, adherence support, and pharmacovigilance, ensuring that endocrine complications are addressed without compromising cancer therapy.

Looking ahead, future research should focus on predictive biomarkers, genetic susceptibility, and personalized monitoring strategies to identify patients at greatest risk. Long-term survivorship studies are also needed to evaluate the chronic impact of thyroid dysfunction on cancer outcomes and quality of life. Ultimately, integrating endocrine vigilance into oncology practice will allow clinicians to maximize the therapeutic benefits of ICIs while minimizing their endocrine toxicity, thereby advancing both patient safety and treatment efficacy.

FUTURE DIRECTIONS:

Despite significant advances in understanding immune checkpoint inhibitor (ICI)-induced thyroid dysfunction, several gaps remain that warrant further investigation. Future research should focus on predictive, preventive, and personalized strategies to optimize patient outcomes while preserving the oncologic benefits of ICIs.

1. Predictive Biomarkers

- Identification of reliable biomarkers, such as baseline thyroid autoantibodies, cytokine profiles, or genetic markers (e.g., HLA polymorphisms), could help stratify patients at risk for thyroid dysfunction.
- Integration of immune signatures and tumor microenvironment analysis may clarify why certain patients develop endocrine irAEs while others do not.

2. Personalized Monitoring Strategies

- Current guidelines recommend routine thyroid function testing every 4–6 weeks, but individualized schedules based on risk stratification could improve efficiency.
- Development of digital health tools and patient-centered dashboards may facilitate real-time monitoring and early detection of thyroid dysfunction.

3. Mechanistic Insights

- Further studies are needed to delineate the precise immunological pathways underlying thyroid injury, including the role of CD8+ T-cell infiltration, cytokine cascades, and autoantibody involvement.
- Comparative research across different ICI classes and combination regimens could clarify agent-specific mechanisms and risks.

4. Survivorship and Long-Term Outcomes

- Longitudinal studies are required to assess the chronic impact of thyroid dysfunction on cancer survivors, including metabolic health, cardiovascular risk, and neurocognitive function.
- Evaluating the relationship between thyroid irAEs and improved oncologic outcomes may provide insights into the dual role of immune activation in both toxicity and efficacy.

5. Multidisciplinary Care Models

- Expanding the role of pharmacists, endocrinologists, and primary care providers in oncology teams will be essential for comprehensive management.
- Structured survivorship programs that integrate endocrine follow-up can improve quality of life and reduce long-term morbidity.

6. Therapeutic Innovation

- Research into preventive interventions, such as prophylactic monitoring or early levothyroxine initiation in high-risk patients, may reduce morbidity.
- Exploration of immunomodulatory strategies that preserve antitumor efficacy while minimizing endocrine toxicity could redefine future treatment paradigms.

REFERENCES:

1. Karaviti D, Kani ER, Karaviti E, Gerontiti E, Michalopoulou O, Stefanaki K, et al. Thyroid disorders induced by immune checkpoint inhibitors. *Endocrine*. 2024;85(1):67–79.
2. Zhan L, Feng H, Liu H, Guo L, Chen C, Yao X, et al. Immune checkpoint inhibitors-related thyroid dysfunction: epidemiology, clinical presentation, possible pathogenesis, and management. *Front Endocrinol*. 2021;12:649863.
3. Mao X, Mao C, Liu J, Wang X, Mao Y. Immune checkpoint inhibitor-induced thyroiditis and its potential mechanisms. *Front Endocrinol*. 2025;16:1584675.
4. Hammerstad SS, Lee HJ, Tomer Y, Stefan-Lifshitz M. Immune checkpoint inhibitors associated thyroiditis: mechanisms and clinical outcomes. *J Endocrinol Invest*. 2025;48(5):2001–12.
5. Stelmachowska-Banas M, Czajka-Oraniec I. Immune checkpoint inhibitors and thyroid dysfunction: epidemiology, clinical manifestations, and management. *Front Endocrinol*. 2021;12:649863.
6. Velez MA, Kang ES, Thompson CA, Lind-Lebuffe J, Shen C, Park SJ, et al. Adequacy of immune checkpoint inhibitor–associated thyroid function monitoring after therapy. *JCO Oncol Pract*. 2025;22(6):306–13.
7. Delivanis DA, Gustafson MP, Bornschlegl S, Merten MM, Kottschade L, Withers S, et al. Pembrolizumab-induced thyroiditis: comprehensive immunologic analysis in a prospective cohort. *J Clin Endocrinol Metab*. 2017;102(6):1930–40.
8. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-mediated thyroid dysfunction during PD-1 blockade in patients with non-small cell lung cancer. *Ann Oncol*. 2017;28(3):583–9.
9. Kurimoto C, Inaba H, Ariyasu H, Iwakura H, Ueda Y, Uraki S, et al. Predictive and diagnostic biomarkers for immune checkpoint inhibitor-related thyroid dysfunction. *Front Endocrinol*. 2020;11:528.
10. Muir CA, Clifton-Bligh RJ, Long GV, Scolyer RA, Lo SN, Carlino MS, et al. Thyroid immune-related adverse events following immune checkpoint inhibitor treatment. *J Clin Endocrinol Metab*. 2021;106(2):e370–81.
11. Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4(2):173–82.
12. Kotwal A, Haddox C, Block M, Kudva YC. Immune checkpoint inhibitors: an emerging cause of thyroid dysfunction. *Nat Rev Endocrinol*. 2020;16(6):295–304.
13. de Filette J, Jansen Y, Schreuer M, Everaert H, Velkeniers B, Neyns B, et al. Incidence of thyroid-related adverse events in melanoma patients treated with pembrolizumab. *J Clin Endocrinol Metab*. 2016;101(11):4431–9.

14. Caturegli P, Di Dalmazi G, Lombardi M, Larman HB, Larman T, Taverna G, et al. Hypophysitis secondary to cytotoxic T-lymphocyte–associated protein 4 blockade: insights into pathogenesis from an autopsy series. *Am J Pathol*. 2016;186(12):3225–35.

15. Byun DJ, Wolchok JD, Rosenberg LM, Girotra M. Cancer immunotherapy—immune checkpoint blockade and associated endocrinopathies. *Nat Rev Endocrinol*. 2017;13(4):195–207.

16. Tan MH, Iyengar R, Mizokami-Stout K, Yentz S, MacEachern MP, Shen LY, et al. Spectrum of immune checkpoint inhibitor-induced endocrinopathies in cancer patients. *Cancer Med*. 2019;8(3):653–64.

17. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. *Endocr Rev*. 2019;40(1):17–65.

18. Kimbara S, Fujiwara Y, Iwama S, Ohashi K, Ito M, Yamazaki N, et al. Association of antithyroid antibodies with the development of thyroid dysfunction induced by nivolumab. *Cancer Sci*. 2018;109(11):3583–90.

19. Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to immune checkpoint blockade. *Sci Transl Med*. 2014;6(230):230ra45.

20. Min L, Vaidya A, Becker C. Endocrine side effects of cancer immunotherapy. *Endocr Rev*. 2020;41(2):373–88.