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# Endocrinopathies from checkpoint inhibitors: Incidence, outcomes, and management

## ABSTRACT

Immune checkpoint inhibitors are used more and more to treat several types of cancer, significantly extending cancer-free survival. However, concerns are growing about their toxic effects, which are many and varied. Endocrinopathies are some of the most frequently reported adverse effects, and thyroid dysfunction is the most common of these. Here, we review the incidence and severity of each immune checkpoint inhibitor-related endocrinopathy, possible factors related to toxicity risk, and principles of management.

## KEY POINTS

The US Food and Drug Administration has so far approved 9 immune checkpoint inhibitors, which variously target programmed cell death protein 1, programmed cell death ligand 1, cytotoxic T-lymphocyte-associated protein 4, and lymphocyte activation gene 3.

Checkpoint inhibitor drugs have revolutionized cancer treatment, as they unleash the power of the immune system to destroy cancer cells.

Professional societies have issued guidelines for surveillance and treatment of immune checkpoint inhibitor-associated endocrinopathies.

With time and further research, strategies for predicting, preventing, and treating these toxicities should emerge.

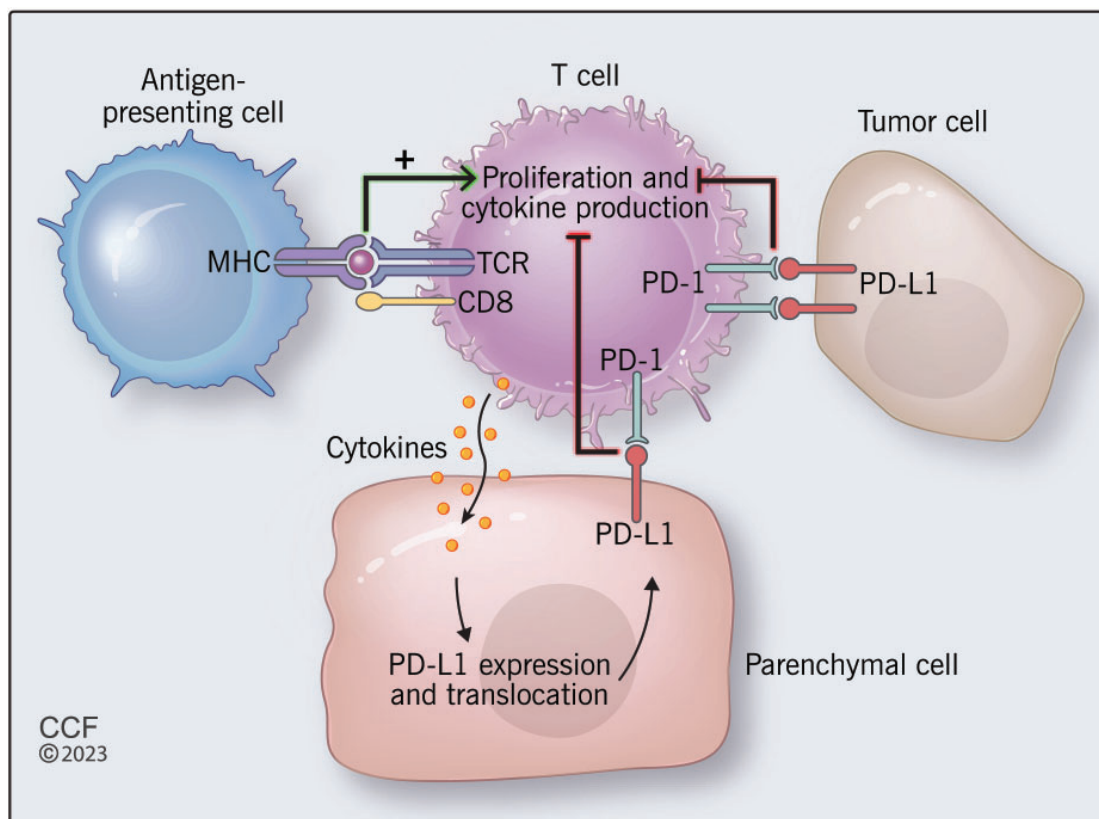
THE DISCOVERY OF THE MOLECULAR mechanisms by which cancer cells evade the immune system has brought about a revolution in cancer immunotherapy. In the past, immunotherapy had very limited success, but unmasking these mechanisms paved the way toward the invention of immune checkpoint inhibitors—monoclonal antibodies that block key regulators of the immune system. Cancer cells typically target these regulators, suppressing the immune response against them and thereby helping them evade the immune system.

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Starting with ipilimumab in 2011, the US Food and Drug Administration (FDA) has so far approved 9 immune checkpoint inhibitors that target the following proteins:

- Programmed cell death protein 1 (PD-1, less commonly known as CD279)
- Programmed cell death ligand 1 (PD-L1, also known as CD274)
- Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4, also known as CD152)
- Lymphocyte activation gene 3 (LAG-3).

These drugs have become mainstays in treating a variety of tumors, including those of the lung, esophagus, stomach, colon, liver, kidney, bladder, uterus, and skin.<sup>1</sup> In fact, their efficacy has overtaken that of standard treatments, prolonging survival even in patients with tumors of advanced stage.



**Figure 1.** Proposed mechanism of the programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 pathway (PD-L1). (MHC = major histocompatibility complex ; TCR = T-cell receptor.)

Nevertheless, concerns about the immune-related adverse effects of these drugs have been growing.<sup>2</sup> The excessive activation of the immune system by these drugs causes dermatologic, endocrine, gastrointestinal, pulmonary, and other toxicities.<sup>2</sup>

In particular, endocrinopathies occur in roughly 10% of patients who receive immune checkpoint inhibitors.<sup>3</sup> Hypopituitarism, type 1 diabetes mellitus, and thyroid and adrenocortical dysfunction are the most common disorders that checkpoint inhibitors cause, depending on the drug.<sup>4</sup> The severity of these events has prompted researchers to look for adjuncts to minimize the toxicities while maintaining the efficacy of the drugs.<sup>3</sup>

Here, we review the mechanisms of action of the currently approved immune checkpoint inhibitors, the incidence of their associated endocrinopathies, the short-term and long-term outcomes of these adverse effects, and their management based on current guidelines.

## MECHANISM OF ACTION OF IMMUNE CHECKPOINT INHIBITORS

### The PD-1/PD-L1 pathway

PD-1, a cell-surface protein, was discovered by Ishida and colleagues<sup>5</sup> while studying apoptosis. It is most notably expressed by activated cytotoxic T cells after recognizing non-self antigens presented by major histocompatibility complexes of antigen-presenting cells.<sup>6</sup> The interaction of the T-cell receptor and the major histocompatibility complex results in release of cytokines that trigger expression of PD-L1 by local parenchymal tissue.<sup>7</sup> Parenchymal PD-L1 then binds T-cell PD-1 to transmit an inhibitory signal to the T cell and induce peripheral immune tolerance, so that healthy parenchymal tissue is protected from inflammatory destruction.<sup>6,7</sup>

Tumor cells manipulate this pathway by overexpressing PD-L1, so that T cells become exhausted and apoptosis is inhibited (**Figure 1**).<sup>6</sup> Therefore, blocking either PD-1 or PD-L1 enhances cytotoxic T-cell

**TABLE 1**  
**Common Terminology Criteria for Adverse Events (CTCAE)**

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asymptomatic or mild symptoms or change in affected chronic condition from baseline (eg, diabetes mellitus)	Moderate symptoms; limiting age-appropriate instrumental activities of daily living	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated	Death

Adapted from reference 18.

activity against PD-L1–expressing cells, including those of both the tumor and the parenchyma.

As of today, 4 PD-1 inhibitors (nivolumab, pembrolizumab, cemiplimab, and dostarlimab) and 3 PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab) have been approved by the FDA.<sup>4</sup>

### The CTLA-4 pathway

CTLA-4 is another T-cell surface protein that transmits inhibitory signals when bound by its ligands.<sup>8</sup> It is homologous to T-cell receptor, which, in contrast, transmits stimulatory signals when bound. CTLA-4 binds the T-cell receptor ligands CD80/86 on antigen-presenting cells with greater affinity and avidity than T-cell receptor.<sup>9</sup> Thus, it can outcompete T-cell receptor for its ligands and prevent its downstream stimulatory signal.

While this pathway is not manipulated by tumor cells, blocking CTLA-4 to ease T-cell receptor-CD80/86 binding enhances T-cell activation and cytotoxic activity against tumors.<sup>9</sup> Ipilimumab remains the only FDA-approved CTLA-4 inhibitor to date.<sup>4</sup>

### The LAG-3 pathway

The role of the LAG-3 pathway in tumorigenesis has been extensively studied since its discovery more than 30 years ago.<sup>10</sup>

LAG-3 is a transmembrane protein that binds major histocompatibility complex class II, suppressing proliferation and activation of T cells.<sup>10</sup> This protein is also expressed on B cells and therefore has similar regulatory effects on B cells and natural killer cells.<sup>10</sup> Naive T cells express low levels of LAG-3, but tumor antigens cause an increase in activity of LAG-3, leading to T-cell exhaustion.<sup>10</sup>

Inhibiting the LAG-3 pathway restores T-cell function, thereby leading to increased accumulation

and effector function on tumor cells.<sup>10</sup> Of note, combining LAG-3 inhibition with PD-1 blockade reduces tumor burden synergistically.<sup>11</sup>

In March 2022, the FDA approved the first human LAG-3 inhibitor (relatlimab), to be used in combination with nivolumab to treat unresectable or metastatic melanoma, based on data from a randomized phase 2 and 3 study.<sup>12</sup>

## ■ INCIDENCES OF ENDOCRINE IMMUNE-RELATED ADVERSE EVENTS

### Pituitary dysfunction

Hypopituitarism is a rare endocrine disorder that can result from disease of the pituitary gland or the hypothalamus. Hypophysitis, ie, inflammation of the pituitary gland, usually leads to pituitary enlargement<sup>13,14</sup> and has been reported to be a major cause of immune checkpoint inhibitor-mediated hypopituitarism, although some authors use the terms hypopituitarism and hypophysitis interchangeably.<sup>15</sup> As the use of immune checkpoint inhibitors has increased in recent years, so has the incidence of hypophysitis.<sup>13,14</sup>

Immune checkpoint inhibitor-induced hypophysitis affects the anterior pituitary (which secretes follicle-stimulating hormone, luteinizing hormone, adrenocorticotrophic hormone, thyroid-stimulating hormone, prolactin, endorphins, and growth hormone) more often than it affects the posterior pituitary (which secretes antidiuretic hormone and oxytocin),<sup>16,17</sup> and most patients have multiple hormonal deficiencies. Barroso-Sousa et al<sup>3</sup> reported in a meta-analysis that 36 (39%) of 92 patients on immune checkpoint inhibitor regimens who developed hypophysitis had symptoms of grade 3 or higher on the Common Terminology Criteria for Adverse Events (CTCAE) scale (Table 1).<sup>3,18</sup>

**Central hypothyroidism** is the most frequent complication, followed by **hypogonadism**. This is distinctive with the CTLA-4 inhibitor ipilimumab, suggesting that CTLA-4 is expressed preferentially by the thyrotropin-secreting and gonadotropin-secreting cells.<sup>16,19</sup>

**Central adrenal insufficiency** is also common and is concerning, as it can lead to life-threatening adrenal crisis.

**Hypoprolactinemia:** Prolactin levels are usually low; hyperprolactinemia is uncommon.<sup>17</sup>

**Growth hormone deficiency** is rare, as the growth hormone axis is usually spared.<sup>14</sup>

**Diabetes insipidus** is a very rare feature of hypopituitarism.<sup>20</sup>

### Risk factors for pituitary dysfunction

Male sex seems to play a role in incidence, with higher rates reported in men.<sup>16,17,21</sup> Although this male predominance may be confounded by the sex discrepancies associated with melanoma (which also occurs more frequently in men, and which is treated with ipilimumab), the rates of hypophysitis still appear to be higher after taking this into account.<sup>16,17</sup> This is in contrast to other etiologies of autoimmune hypophysitis, which are more common in women.<sup>14</sup>

Age is a contributing factor, with people over age 65 having a higher risk.<sup>16,17</sup>

**Ipilimumab.** Immune checkpoint inhibitor-induced hypophysitis-hypopituitarism is almost exclusively associated with the CTLA-4 inhibitor ipilimumab, and it appears to be the most common endocrinopathy associated with this drug,<sup>14</sup> with incidences in the range of 10% to 15% reported.<sup>16,17</sup> Cumulative dosage or cycle frequency do not appear to affect the incidence significantly.<sup>16</sup>

However, the incidence is significantly higher with nivolumab-ipilimumab combination therapy (about 8%) than with ipilimumab alone (about 4%).<sup>3</sup>

Hypophysitis-hypopituitarism occurs significantly less often with PD-1 inhibitors than with ipilimumab, and the presentations may drastically differ between the 2 drug classes, strongly suggesting independent pathways.<sup>22</sup> For instance, gland enlargement and combined axis dysfunction are more common in those treated with ipilimumab, whereas secondary adrenal insufficiency with subtle gland enlargement is more common with PD-1 inhibitors.<sup>22</sup>

**Human leukocyte antigen (HLA)-DR15.** Due to the pathogenic nature of immune-related adverse events in general, predisposing HLA variants have been researched as a way to predict adverse outcomes.

So far, studies have revealed an association between HLA-DR15 and the development of immune checkpoint inhibitor-induced secondary insufficiency.<sup>23</sup>

### Course of hypopituitarism

The median time of onset of hypophysitis-hypopituitarism is 8 to 10 weeks after initiating treatment,<sup>16,17</sup> although this can vary by as much as 4 months.<sup>24</sup> Unlike other forms of autoimmune hypophysitis, it is usually not accompanied by visual disturbances.

Pituitary enlargement and hypophysitis usually resolve, but hypopituitarism can persist (with or without steroid treatment) and may be permanent depending on the hormonal axis involved.<sup>24</sup> For example, the thyroid axis may recover in the long term, but recovery of corticotroph cell function is rare. Therefore, quality of life after immune checkpoint inhibitor therapy poses a major issue for patients with secondary adrenal insufficiency.

### Thyroid dysfunction

Thyroid dysfunction is the most common endocrine immune-related adverse event associated with immune checkpoint inhibitor therapy. Dysfunction can be in the form of either thyrotoxicosis or hypothyroidism, but the latter is the more common presentation.<sup>13</sup>

Although some authors use the terms *thyrotoxicosis* and *hyperthyroidism* interchangeably, we would like to clarify the definitions. Hyperthyroidism is thyroid hormone overproduction caused by an intrinsic pathological excess in thyroid hormone synthesis and secretion by the thyroid gland, and examples are Graves disease, toxic adenoma, and toxic multinodular goiter. Thyrotoxicosis, however, encompasses all causes of thyroid hormone excess, including hyperthyroidism and pathologies that result in a temporary excess release of thyroid hormone, as we will describe later.

Thyrotoxicosis as the primary presentation is predominantly related to silent or destructive thyroiditis, and in most of these cases, hypothyroidism ensues shortly thereafter (median time 42 days).<sup>14,25</sup> Therefore, many thyrotoxic adverse events may go undetected without close monitoring.<sup>14</sup> For example, in a study by Lee et al<sup>25</sup> of 45 patients who developed thyroid dysfunction after anti-PD-1 monotherapy or combination therapy, thyrotoxicosis was the initial presentation in 78% of patients, although 80% of those patients subsequently developed hypothyroidism.<sup>25</sup> A study by Lu et al<sup>26</sup> showed that only 9.3% of hypothyroidism cases reported to the FDA reporting system manifested with destructive thyroiditis (initially presenting as hyperthyroidism).



Graves disease is also an uncommon presentation of immune checkpoint inhibitor-induced thyrotoxicosis.<sup>13</sup> However, due to inconsistency in reporting, the incidence of Graves disease as an adverse event may be underreported.<sup>13,27</sup>

Barroso-Sousa et al,<sup>3</sup> in a meta-analysis of 38 randomized controlled trials, calculated the overall incidence of hypothyroidism to be 6.6% (95% confidence interval 5.5%–7.8%) and the incidence of thyrotoxicosis to be 2.9% (95% confidence interval 2.4%–3.7%).<sup>3,14</sup>

Most recently, Lu et al,<sup>26</sup> using data from the US Food and Drug Administration Adverse Event Reporting System (FAERS) from 2011 until 2020, reported a much lower incidence of thyroid dysfunction—ie, 2.6%. Of these cases, 62% were hypothyroidism, 22.7% were hyperthyroidism, and 15.3% were reported as thyroiditis without thyroid function information.<sup>26</sup> The authors accounted for this discrepancy as simply due to differences in study design and reporting, as clinical trials typically have closer follow-up and therefore more frequent reporting. Also, the FAERS reporting system may not capture less-severe adverse events. However, recent clinical data strongly suggest that the incidence of immune checkpoint inhibitor-induced thyroiditis and hypothyroidism is increasing,<sup>28,29</sup> which is to be expected given the increased screening and reporting as well as increased use of immune checkpoint inhibitors.

Regarding severity, most of the thyroid-related adverse events are either asymptomatic (subclinical) or cause mild or moderate symptoms (CTCAE grade 1 or 2), with less than 1% leading to severe symptoms, hospitalization, or death (CTCAE grade 3 or higher).<sup>30</sup>

### Risk factors for thyroid dysfunction

**Women** may have a higher risk of thyroid dysfunction than men.<sup>15,26,31,32</sup> An explanation may be related to sex-hormone-mediated immune regulation, or possibly sex-specific autoimmunity.<sup>33</sup>

**Elevated body mass index** may also be associated with increased risk, earlier onset of symptoms, and overt hyperthyroidism.<sup>15,31</sup>

**Advanced age** may also increase the risk of severe thyroid dysfunction, leading to increased rates of hospitalization, morbidity, and death.<sup>26</sup>

**Tyrosine kinase inhibitor use** may also predispose to immunotherapy-related thyroid dysfunction,<sup>30,34</sup> although tyrosine kinase inhibitors can also independently cause thyroid dysfunction.<sup>35</sup>

**Biomarkers** that may predict thyroid-related adverse events are elevated levels of thyroid-stimulating hormone, thyroid autoantibodies, thyroglobulin, and cytokines.<sup>15,31,36</sup> In addition, Kurimoto et al<sup>36</sup> demonstrated that higher serum levels of interleukin 1-beta, interleukin 2, and granulocyte-macrophage colony-stimulating factor at baseline and early decreases in interleukin 8, granulocyte colony-stimulating factor, and monocyte chemoattractant protein 1 were significantly associated with thyroid dysfunction ( $P < .5$ ).<sup>36</sup>

**Agent used.** The incidence of thyroid dysfunction strongly depends on the type of agent and whether it is given as monotherapy or combined therapy. For instance, studies by Barroso-Sousa et al<sup>3</sup> and Lu et al<sup>26</sup> clearly demonstrated that the anti-PD-1 class poses the highest risk of thyroid dysfunction. On the other hand, the anti-CTLA-4 agent ipilimumab is associated with the lowest frequency of thyroid dysfunction.

Combination anti-CTLA-4 and anti-PD-1 therapy arguably has the highest risk of thyroid dysfunction. Of note, whereas previous studies consistently reported a higher incidence of thyroid dysfunction with combination anti-CTLA-4–anti-PD-1 therapy than with monotherapy of each class,<sup>3,4</sup> Lu et al recently reported that the incidence of PD-1-related hypothyroidism exceeded that with combination therapy.<sup>26</sup> However, this pattern of more adverse events with combination therapy is not unique to thyroid dysfunction, as discussed above with pituitary dysfunction. Also, higher CTCAE grades of thyroid dysfunction are more frequent with combination therapy.<sup>3,13</sup>

Dose and tumor type are not significantly associated with the incidence of immunotherapy-mediated thyroid dysfunction.<sup>3,13</sup>

### Course of thyroid dysfunction

The time of onset of thyroid dysfunction varies greatly, within the first 15 weeks of therapy in most reported cases,<sup>37</sup> but as early as 7 days or as late as 3 years in others.<sup>14</sup> Also, the time to onset is shorter with combined immunotherapy than with monotherapy.<sup>25</sup>

Most cases of hypothyroidism remain permanent and require long-term levothyroxine replacement therapy.<sup>13,14</sup>

### Pancreatic endocrine dysfunction, diabetes mellitus

The adverse effects of immune checkpoint inhibitor therapy on pancreatic endocrine function manifest in a similar manner to type 1 diabetes mellitus, with low or undetectable C-peptide and elevated autoantibody levels.<sup>14,38</sup>

TABLE 2

**Thyroid dysfunction due to immune checkpoint inhibitors: American Society of Clinical Oncology guideline**

Situation	Action
Screening	Thyroid function tests, ie, thyroid-stimulating hormone (TSH) with or without thyroxine (T4) every 4–6 weeks while on therapy
Asymptomatic hypothyroidism (grade 1), TSH > 4.5 and < 10 mIU/L	Monitor thyroid function tests routinely as above Continue immune checkpoint inhibitor
Symptomatic hypothyroidism (grade 2) or TSH persistently > 10 mIU/L	Start levothyroxine (1.6 µg/kg/day if age < 70; 25–50 µg/day if age > 70 or multiple comorbidities); monitor TSH every 6–8 weeks until TSH is at goal, then every 6–12 months unless symptoms change Consider holding immune checkpoint inhibitor until symptoms resolve Consider endocrine consultation for challenging presentation or for hormonal therapy
Severely symptomatic hypothyroidism (grade 3 or 4)	Hold immune checkpoint inhibitor until symptoms resolve Hospital admission usually required Endocrine consultation recommended to assist with rapid hormone replacement Hydrocortisone should be given in the event central hypothyroidism is considered Start on chronic levothyroxine therapy and monitor as above on discharge.
Asymptomatic or mildly symptomatic thyrotoxicosis (grade 1)	Continue immune checkpoint inhibitor Start beta-blocker Monitor TSH and T4 every 2–3 weeks after diagnosis for possible hypothyroidism transition (and treat as for primary hypothyroidism) Consider endocrine consult for persistent thyrotoxicosis (> 6 weeks)
Mildly symptomatic thyrotoxicosis (grade 2)	Consider holding immune checkpoint inhibitor until symptoms improve Consider endocrine consultation Start on beta-blockers Refer to endocrinologist for persistent thyrotoxicosis (> 6 weeks) for additional workup and possible medical thyroid suppression
Severely symptomatic thyrotoxicosis (grade 3 or 4)	Hold immune checkpoint inhibitor until symptoms resolve Endocrine consult for all patients Start on beta-blocker Hospitalization with endocrine consultation to be considered in severe cases to guide medical therapy

Adapted from reference 49.

Incidence rates have been reported to be between 0.2% and 0.9%, with 0.1% being CTCAE grade 3 or higher.<sup>3</sup> However, there are recent reports of a more fulminant course with rapid-onset diabetic ketoacidosis<sup>39,40</sup> associated with a disproportionately normal to mildly elevated hemoglobin A1c.<sup>38,41</sup> Incidence rates are higher with PD-1 inhibitors (nivolumab, pembrolizumab), followed by PD-L1 inhibitors.<sup>38,41</sup> Combination therapy may also increase risk, with a shorter onset of symptoms after initiation of therapy.<sup>38,41</sup>

Akturk et al,<sup>38</sup> in a systematic review and meta-analysis of 71 cases, reported that the mean age of the patients was 61.7 (± 12 years), 55% of cases

were in men, and the median time to onset was 49 days (range 5–448 days) after starting treatment. Half of the patients had autoantibodies at presentation, with a higher incidence of diabetic ketoacidosis and more rapid onset of diabetes mellitus than in patients without autoantibodies. An at-risk *DR* or *DQ* allele as present in 85% of patients tested, similar to the rate in childhood-onset diabetes.<sup>38</sup>

In a systematic review, de Filette et al<sup>41</sup> reported comparable results, with similar incidences of diabetic ketoacidosis (71%) and islet autoantibodies (53%). However, fewer patients (65%) had susceptible HLA genotypes. These findings suggest a role of allele

TABLE 3

### Hypopituitarism due to immune checkpoint inhibitors: American Society of Clinical Oncology guideline

Situation	Action
<b>Screening and workup</b>	Routine thyroid function tests as outlined in Table 2 If central hypothyroidism is suspected, evaluate morning adrenocorticotrophic hormone (ACTH) and cortisol as well as electrolytes ACTH stimulation testing can be falsely negative early in hypophysitis, as adrenal reserve declines slowly after pituitary stimulation is lost
<b>Asymptomatic or mild symptoms (grade 1)</b>	Consider holding immune checkpoint inhibitor until patient is stabilized on hormone replacement Endocrine consultation Initiate hormonal replacement for affected axis Adrenal insufficiency: corticosteroid replacement (hydrocortisone 15–20 mg in divided doses) No adrenal insufficiency: consider lower steroid dosing (average daily dosing over 2 months < 7.5 mg) due to report of reduced survival on higher dosing Initiate other hormone replacement after steroid initiation and only after adrenal insufficiency is corrected, to avoid crisis
<b>Moderate symptoms (grade 2)</b>	Consider holding immune checkpoint inhibitor until the patient is stabilized on hormone replacement Endocrine consultation Consider oral pulse-dose steroid therapy in patients with magnetic resonance imaging evidence of swelling or threatened optic chiasm compression; taper over 1 to 2 weeks, then maintenance steroid therapy Other hormonal replacement therapy as above
<b>Severe symptoms (grade 3 or 4)</b>	Hold immune checkpoint inhibitor until patient is stabilized on hormone replacement Endocrine consultation Hospitalize or refer to emergency department for normal saline (at least 2 L) and monitored free water replacement if the patient has diabetes insipidus Intravenous stress steroids (initial dosing: hydrocortisone 50–100 mg every 6 hours), then oral pulse-dose therapy tapered over 1–2 weeks in patients with magnetic resonance imaging evidence of significant swelling, optic chiasm compression, severe headache, or visual changes Taper stress-dose steroids to oral maintenance dose over 5–7 days Other maintenance therapy as above Patients should have a medical alert device as well as education on stress-dosing for sick days, when to seek medical attention for impending adrenal crisis, and use of emergency steroid injectables

Adapted from reference 49.

screening in patients who may be at risk of immune checkpoint inhibitor-induced diabetes.

As in childhood-onset type 1 diabetes, lifelong insulin therapy is needed, and unlike other immune checkpoint inhibitor endocrinopathies, pancreatic dysfunction does not respond to immunosuppressive therapy.<sup>42</sup>

#### Adrenal gland dysfunction

Immune checkpoint inhibitor-associated primary adrenal insufficiency is an infrequent manifestation of immune-related adverse events, accounting for less than 2%.

Barroso-Sousa et al,<sup>3</sup> in their meta-analysis and systematic review, reported only 43 cases of any grade primary adrenal insufficiency among 5,831 patients

(0.7%), of which 14 (0.3%) were grade 3 or higher. In another study, among 256 patients who received ipilimumab, 2 cases of primary adrenal insufficiency (0.8%) were observed.<sup>43</sup>

Grouthier et al<sup>44</sup> reported that, of a total of 50,108 immune checkpoint inhibitor-associated adverse events (reported using the World Health Organization's pharmacovigilance database of individual case safety reports over a decade), there were 451 cases of primary adrenal insufficiency, of which 45 were "definite" and 406 "possible." A small majority (51.8%) of the cases were in men, with a median age of 66 years. Most patients had received immune checkpoint

TABLE 4

**Adrenal dysfunction due to immune checkpoint inhibitors:  
American Society of Clinical Oncology guideline**

Situation	Action
<b>Screening and workup</b>	No screening recommended Workup for suspected adrenal insufficiency includes morning adrenocorticotrophic hormone (> 2 times the upper limit of normal), cortisol (< 3 µg/dL), basic metabolic panel, renin, and aldosterone Adrenocorticotrophic hormone testing can be considered for indeterminate results Rule out other causes such as infection or metastatic disease
<b>Asymptomatic or mild symptoms (grade 1)</b>	Consider holding the immune checkpoint inhibitor until the patient is stabilized on hormone replacement Endocrine consultation Start hydrocortisone treatment (15–20 mg in divided doses) and titrate to maximum 30 mg/day for residual adrenal insufficiency Most primary adrenal insufficiency cases will also require fludrocortisone (starting dose 0.1–0.5 mg/day) Patients should have a medical alert device as well as education on stress-dosing for sick days, when to seek medical attention for impending adrenal crisis, and use of emergency steroid injectables
<b>Moderate symptoms (grade 2)</b>	Consider holding immune checkpoint inhibitor until the patient is stabilized on hormonal replacement Endocrine consultation Initiate outpatient corticosteroid treatment 2–3 times the maintenance dose (hydrocortisone 30–50 mg/day; prednisone 20 mg/day) to manage acute symptoms and decrease stress dosing after 2 days Initiate fludrocortisone as above Patient education as above
<b>Severe symptoms (grade 3 or 4)</b>	Hold the immune checkpoint inhibitor until the patient is stabilized on hormonal replacement Endocrine consultation For inpatient management, normal saline (at least 2 L) with intravenous stress-dose steroids (initial dosing: hydrocortisone 50–100 mg every 6 hours), then taper to oral maintenance doses over 5–7 days Maintenance therapy as above Patient education as above

Adapted from reference 49.

inhibitor monotherapy (nivolumab 44.3%, pembrolizumab 11.7%, and ipilimumab 23.6%), and 17.9% had received combination therapy. The median time to onset was 120 days (range 6–576).<sup>44</sup>

Immune checkpoint inhibitor-associated primary adrenal insufficiency is associated with significant rates of morbidity (> 90% of cases are severe) and mortality (7.3%). Mortality rates were similar in the subgroups receiving combination therapy vs monotherapy.<sup>44</sup>

Melanoma recurrence may also be a concern, due to persistently elevated adrenocorticotrophic hormone and melanocyte-stimulating hormone levels, although no studies to date have fully investigated this theory.<sup>45</sup>

### Other endocrinopathies

Primary hypoparathyroidism,<sup>46</sup> lipodystrophy,<sup>47</sup> and polyendocrine syndrome<sup>48</sup> have been reported in case reports, but further characteristics are yet to be determined.

### GUIDELINES FOR MANAGING ENDOCRINOPATHIES

The American Society of Clinical Oncology,<sup>49</sup> the National Comprehensive Cancer Network,<sup>50</sup> and the Society of Immunotherapy of Cancer<sup>51</sup> have published practice guidelines on the recognition and management of immune checkpoint inhibitor-related endocrinopathies. The guidelines have similarities, but those of the American Society of Clinical Oncology are the most comprehensive, addressing acute management by CTCAE grade as well as when to consider endocrinology referral for thyroid dysfunction (Table 2), hypopituitarism (Table 3), adrenal insufficiency (Table 4), and diabetes (Table 5).<sup>49</sup>

The American Association of Clinical Endocrinology<sup>52</sup> has also published a clinical review on the evaluation and management of immune checkpoint inhibitor-mediated endocrinopathies, which shares a similar approach. However, it recommends a low threshold for endocrinology referral in the event of



**TABLE 5**  
**Diabetes due to immune checkpoint inhibitors:**  
**American Society of Clinical Oncology guideline**

Situation	Action
<b>Screening and workup</b>	Screening glucose at baseline and with each treatment cycle while on therapy and at follow-up visits for at least 6 months Monitor symptoms for hyperglycemia Other laboratory tests include urine or serum ketones (or both), anion gap on a metabolic panel, anti-glutamic acid decarboxylase antibody, anti-islet cell antibodies, C-peptide
<b>Asymptomatic or mild symptoms (grade 1), or type 2 diabetes with fasting glucose &lt; 160 mg/dL and no new evidence of ketoacidosis or pancreatic autoimmunity</b>	Can continue immune checkpoint inhibitor with close clinical follow-up Refer to primary care physician for diabetes management
<b>Moderate symptoms (grade 2), or type 2 diabetes with fasting glucose &gt; 160–250 mg/dL and no new evidence of ketoacidosis or pancreatic autoimmunity</b>	May hold immune checkpoint inhibitor until glucose control is obtained Urgent endocrine consultation for any patient with new-onset checkpoint inhibitor-associated diabetes Initiate insulin Refer to emergency department if unable to initiate therapy or if urgent outpatient specialist evaluation is unavailable
<b>Severe symptoms (grade 3 or 4), or worsening glucose, glucose &gt; 500 mg/dL, ketoacidosis, or other metabolic abnormality</b>	Hold immune checkpoint inhibitor until glucose control is obtained to levels and symptoms similar to grade 1 Admit for diabetic ketoacidosis, volume and electrolyte resuscitation, and insulin initiation Endocrine consultation recommended for all patients Insulin therapy appropriate for all patients

Adapted from reference 49.

any laboratory derangement suggesting endocrine organ dysfunction. This includes thyroid dysfunction, as closer monitoring and further tests for adrenal insufficiency may be warranted.

Generally, unless patients have moderate or severe symptoms (CTCAE grade 3 or 4), immune checkpoint inhibitor therapy can continue throughout the endocrine adverse event. Permanently stopping these drugs is not routinely recommended,<sup>49</sup> as most endocrinopathies are long-term and are treatable. This is unlike other immune-related adverse events (eg, pulmonary toxicities), for which more aggressive temporary or permanent discontinuation is recommended.<sup>49</sup>

Also, unlike in other organ-specific immune-related adverse events, steroids are not routinely recommended except in hypophysitis and primary adrenal insufficiency. High-dose steroids do not improve recovery rates in patients with hypophysitis<sup>53</sup> and have been associated with worse outcomes.<sup>54</sup> Therefore, high-dose steroids are reserved for patients

with associated mass-effect symptoms. Similar outcomes have also been shown in patients with immune checkpoint inhibitor-induced diabetes,<sup>42</sup> and steroids are generally avoided.

Dehydroepiandrosterone replacement is controversial. However, deficiency can be tested and treated in women with low libido or energy who are judged to be otherwise well-replaced for other hormonal deficiencies.

The adverse effects of immune checkpoint inhibitors do have an upside: they may predict that the drug is working on the cancer, and the patient can expect prolonged recurrence-free survival.<sup>55</sup> In particular, endocrine immune-related adverse events (particularly thyroid dysfunction) may have the strongest associations with improved clinical outcomes.<sup>56</sup> These correlations therefore further support the consideration of not discontinuing immune checkpoint inhibitor therapy once the adverse events are manageable.

## ■ AN EMERGING PICTURE

With the increased use of immune checkpoint inhibitors in cancer treatment, more precise reporting of their extensive endocrine immune-related adverse events is occurring. This will give a clearer picture of the true incidences and characteristics of each endocrinopathy and will help inform further updated guidelines for pretreatment investigations, monitoring, and management. Prolonged routine posttreatment monitoring should also be considered, as some adverse effects can occur many months after discontinuation.

Interspecialist planning and monitoring with endocrinologists and oncologists should also be considered, as this may allow earlier hormone-replacement therapy, as well as immunotherapy de-escalation for those with moderate to severe events.

Primary care physicians should be aware of the

need to perform routine screening and surveillance investigations, when to consider endocrinology referral, and when to consider urgent or emergent care referral. Patients should be routinely and extensively counseled on the endocrine adverse effects, including the common signs and symptoms, when to seek urgent care, and the likelihood of indefinite hormonal replacement therapy should these events occur.

Finally, larger prospective studies are needed to answer questions pertaining to risk factors (age, sex, autoimmune markers), interventions to reduce risk of endocrinopathies, and the risk of recurrence after restarting therapy. ■

## ■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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