Immune Checkpoint Inhibitor-induced Thyroid Dysfunction Is Associated with Higher Body Mass Index

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Context: Obesity is a proinflammatory metabolic state that may play a role in the development of immune-related adverse events (irAEs) associated with immune checkpoint inhibitor therapy.

Objective: To characterize the association between body mass index (BMI) and thyroid irAEs.

Methods: We performed a single-center, retrospective analysis of 185 cancer patients treated with anti-PD-1/L1 from January 2014 to December 2018. Patients with normal thyroid function at baseline and available BMI were included.

Main outcome measures: The primary endpoint was difference in BMI in patients who developed overt thyroid dysfunction versus those who remained euthyroid following anti-PD-1/L1 initiation. Additional endpoints included any (overt or subclinical) thyroid dysfunction, overt thyrotoxicosis or overt hypothyroidism, and time to development of dysfunction according to BMI.

Results: Any thyroid dysfunction developed in 72 (38.9%) patients and 41 (22.1%) developed overt thyroid dysfunction. Mean BMI was higher in those with overt thyroid dysfunction versus euthyroid (27.3 ± 6.0 vs 24.9 ± 4.5, \(P = .03\)). Development of overt thyrotoxicosis versus remaining euthyroid was associated with higher BMI (28.9 ± 5.9 vs 24.9 ± 4.5; \(P < .01\)), whereas overt hypothyroidism was not (26.7 ± 5.5 vs 24.9 ± 4.5, \(P = .10\)). Overt thyrotoxicosis developed within 57.5 (interquartile range [IQR] 31.8-78.8) days of treatment in the low-normal BMI group, 38.0 (IQR 26.8-40.5) days in the overweight group, and 23.0 (IQR 21.0-28.0) days in the obese group (\(P = .02\)).

Conclusions: Patients treated with PD-1/L1 inhibitors were more likely to develop thyroid irAEs, specifically overt thyrotoxicosis, with increasing BMI. Overt thyrotoxicosis occurred earlier in obese versus leaner patients. These data highlight the complex interplay between obesity and immune response in immune checkpoint inhibitor-treated patients. (J Clin Endocrinol Metab 105: 1–8, 2020)

Freeform/Key Words: BMI, obesity, immune checkpoint inhibitor, immune related adverse events, thyroid dysfunction, thyroiditis

*These authors contributed equally to this manuscript.

Abbreviations: BMI, body mass index; CI, confidence interval; EMR, electronic medical record; FT3, free 3,5,3′-triiodothyronine; FT4, free thyroxine; GI, gastroenterological; GU, genitourinary; ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; SD, standard deviation; TFT, thyroid function test; TSH, thyrotropin.
immune checkpoint inhibitors (ICIs) have transformed the care of cancer patients, providing therapeutic options for advanced malignancies considered otherwise untreatable. ICIs have been associated with excellent response rates and improved overall survival; however, they are associated with immune-related adverse events (irAEs) that can affect all organ systems (1-10). Endocrinopathies are among the most common irAEs and include hypophysitis, adrenal insufficiency, type 1 diabetes, and, most frequently, thyroid dysfunction (11). Real-world studies have reported thyroid abnormalities including hypothyroidism, hyperthyroidism, and thyroiditis (thyrotoxicosis progressing to hypothyroidism) in up to 50% of patients receiving programmed cell death-1 (PD-1) and programmed cell death-ligand 1 (PD-L1) inhibitors (12-15).

The underlying mechanism of ICI-induced thyroid dysfunction has not yet been fully elucidated and it remains unclear why the thyroid is so frequently affected. Several studies have suggested that hypothyroidism and hyperthyroidism may be different manifestations of the same pathological entity of destructive thyroiditis, resulting from the unleashing of cytotoxic T cells against thyroid antigens (16-18). This, in turn, leads to activation of the humoral response and secondary antibody production (19). It has also been proposed that ICI-induced thyroid dysfunction may simply be unmasking of latent autoimmunity and the presence of thyroid antibodies in up to 18% of the general population (32% of adults age 60+ years) may explain why thyroid irAEs are so common (20-22).

Recent studies have investigated potential risk factors for the development of thyroid irAEs. Specifically, the presence of thyroid autoantibodies at baseline, higher baseline thyrotropin (TSH), and number of ICI treatment cycles have been associated with increased risk (10, 12, 21). Emerging evidence suggests that obesity may also play a role in the development of irAEs (23). Obesity is a low-grade inflammatory metabolic state that has been associated with numerous comorbidities including diabetes, cardiovascular disease, and cancer (24-28). Moreover, a number of studies found a significant correlation between obesity and autoimmune conditions; however, the impact of obesity on the immune response in patients with ICI-induced thyroid dysfunction has not been well characterized (29). In the current study, we aimed to explore the relationship between body mass index (BMI) and thyroid irAEs in patients treated with PD-1 or PD-L1 inhibitors.

### Materials and Methods

We conducted a noninterventional retrospective study utilizing deidentified data from the Hadassah Hebrew-University Medical Center electronic medical record (EMR). Complete medical data are recorded in the EMR, including medical diagnoses, laboratory tests, prescribed medications, and information on all patient medical interactions including outpatient visits, acute medical services, and hospitalizations. Approval was obtained from the Hadassah Medical Center Institutional Review Board and Ethics Committee for the purpose of accessing and analyzing the data. Individual patient informed consent was not required because of the anonymized nature of the patient records.

### Study population

The present study included patients aged 18 years or above with stage III or stage IV lung, gastroenterological (GI), or genitourinary (GU) malignancies who initiated treatment with single agent PD-1 (nivolumab, pembrolizumab) or PD-L1 inhibitor (durvalumab, atezolizumab) from January 1, 2014, to December 31, 2018, at our institution. The index date was defined as the first date of treatment with ICI agent. Patients meeting the inclusion criteria were ≥18 years old with documentation of BMI at index date, who had received treatment with a PD-1/PD-L1 inhibitor according to standard protocols. In addition, documentation of thyroid function tests (TFTs) including TSH, free thyroxine (FT4) and free 3,5,3’-triiodothyronine (FT3) within 3 months prior to the index date and at least 2 measurements post treatment initiation was required. Subjects were excluded if they had a history of thyroid dysfunction prior to the index date, including prior diagnosis of thyroid dysfunction listed in the EMR, previous treatment with antithyroid drugs or levothyroxine, or evidence of abnormal thyroid function tests at baseline. Patients were censored at the date of last contact or date of death.

TFTs were not measured at set intervals. In the initial study years, they were measured per physician discretion; due to increasing awareness of the possibility of thyroid dysfunction due to therapy, frequent tests were taken. In more recent years, with increasing awareness, TFTs were taken more frequently, nearly prior to each treatment cycle.

### Assessment of outcome

The relationship between BMI (as a continuous and a categorical variable) and each of the clinical outcomes was assessed. The primary outcome was the difference in BMI between patients developing overt thyroid dysfunction versus remaining euthyroid. Additional endpoints included the association of BMI with the development of (1) any thyroid dysfunction (overt and subclinical), (2) overt hypothyroidism, (3) overt thyrotoxicosis, and (4) time to development of overt hypothyroidism and overt thyrotoxicosis as a function of BMI category.

### Variables, definitions, derivations, and measurements

Data collected included age, gender, BMI at the index date, history of diabetes, type and stage of malignancy, previous chemotherapy, type of ICI agent (PD-1 vs PD-L1 inhibitor),
and thyroid function tests at baseline—the test most recent to initiation of treatment—and all available measurements post ICI treatment.

BMI was assessed both as a continuous and as a categorical variable. The patients were divided into 3 categories according to baseline BMI: low-normal BMI (≤25), overweight (≥25-30), and obese (≥30), in accordance with World Health Organization criteria (30).

Thyroid outcomes were defined as follows (groups are not mutually exclusive):

1. Any thyroid dysfunction was defined as a TSH value above or below the laboratory-specific range, irrespective of FT4 and FT3 levels during follow-up.
2. Any subclinical thyroid dysfunction was defined as a TSH above the laboratory-specific reference range but <10 mU/L, or a TSH value below the laboratory-specific reference range without a corresponding FT4 or FT3 abnormality.
3. Overt thyroid dysfunction was defined as either overt hypothyroidism or overt thyrotoxicosis. Overt hypothyroidism was defined as either elevated TSH with reduced FT4 and/or FT3 or TSH ≥10 mU/L. Overt thyrotoxicosis was defined as a suppressed TSH with elevated FT4 and/or FT3 levels.
4. Central hypothyroidism was defined as a TSH value below the laboratory-specific reference range with reduced FT4 and/or FT3 or a normal TSH value with a reduced FT4 level.
5. Thyroiditis was defined as subclinical or overt thyrotoxicosis followed by progression to overt hypothyroidism. Patients who developed both thyrotoxicosis and hypothyroidism were considered in the categories of thyroiditis, thyrotoxicosis (overt or subclinical), and hypothyroidism.

Statistical analysis

Baseline characteristics are reported as frequencies and percentages for categorical variables and as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables. All comparisons were made to the euthyroid category. Categorical variables were compared using the chi-squared test and continuous variables were compared using the t-test for parametric variables and the Mann–Whitney U test for nonparametric variables.

The association between the baseline variables and any or overt thyroid dysfunction was assessed using logistic regression. All variables with statistical significance in the unadjusted model were included in the multivariate analysis. Odds ratio and 95% confidence interval (CI) are presented. Within those developing overt thyrotoxicosis or overt hypothyroidism we used the Jonckheere–Terpstra test to compare the time elapsing from treatment to the development of the dysfunction by categorical BMI.

A P < .05 was considered statistically significant. All statistical analyses were conducted using SPSS version 25.0 and R version 3.6.1 for Windows.

Results

Study cohort

We identified a total of 236 patients aged 18 years or older with lung, GI, or GU malignancies who initiated treatment with PD-1 or PD-L1 inhibitors from January 1, 2014, to December 31, 2018. After applying all inclusion and exclusion criteria, 185 patients were included in the study and followed for a median of 12 (IQR 4-23) months (Figure 1).

Baseline characteristics of the overall cohort are presented in Table 1. The study population consisted of 69.2% men, mean age 63.6 ± 14.3 years, with mean BMI of 25.7 ± 5.2 kg/m². Overall, 47.6% had a BMI ≥25 kg/m², and 15.7% had history of diabetes type 2. Mean baseline TSH was 1.8 ± 1.0 mU/L.

Outcomes

Any thyroid dysfunction. A total of 72 (38.9%) patients developed any (subclinical or overt) thyroid dysfunction. Patients who developed any thyroid

![Figure 1. Consort diagram. Abbreviations: GI, gastrointestinal; GU, genitourinary; BMI, body mass index.](https://academic.oup.com/jcem/article-lookup/10.1210/clinem/dgaa458)
dysfunction were of similar age and gender distribution compared with the euthyroid group; however, mean baseline TSH was higher (2.0 ± 1.2 vs 1.6 ± 0.9 respectively, \(P < .01\)). Mean BMI was significantly higher among those developing thyroid dysfunction than in the euthyroid group (27.1 ± 5.8 vs 24.9 ± 4.5 respectively, \(P < .01\); table 2). In multivariate analysis, both baseline BMI and TSH emerged as independent predictors of any thyroid dysfunction (Table 2).

Subclinical thyroid dysfunction without subsequent overt dysfunction was observed in 31 (16.8%) patients. Their mean BMI was significantly higher than the euthyroid group (26.9 ± 5.7 vs 24.9 ± 4.5, \(P = .04\)). No cases of central hypothyroidism were identified.

**Overt thyroid dysfunction.** Among the 185 patients included in the cohort, 41 (22.2%) developed overt thyroid dysfunction (hyper- or hypothyroidism). Patients who developed overt thyroid dysfunction had similar age and gender distribution; however, their mean baseline TSH was higher (2.2 ± 1.2 vs 1.6 ± 0.9, \(P < .01\)) than in those who remained euthyroid (Table 3). Moreover, the mean BMI was significantly higher in those developing overt thyroid dysfunction than in those remaining euthyroid (27.3 ± 6.0 vs 24.9 ± 4.5, \(P = .01\)). Analyzing BMI as a continuous variable revealed a consistent increase in risk of developing overt thyroid dysfunction with increasing BMI, such that for every 1 kg/m², the risk of overt thyroid dysfunction increased by 10.0% (OR = 1.10, 95% CI 1.02-1.18, \(P = .01\); Figure 2). In multivariate analysis, both baseline BMI and TSH emerged as independent predictors of overt thyroid dysfunction (Table 3).

Excluding the 8 patients in the overall cohort with BMI <18.5 kg/m² yielded similar results (data not shown).

**Overt hypothyroidism and overt thyrotoxicosis.** We further analyzed the association of BMI with the development of overt hypothyroidism or overt thyrotoxicosis (Figure 3). Overall, 32 (17.3%) developed overt hypothyroidism and 17 (9.2%) developed overt thyrotoxicosis. BMI was similar in patients who developed overt hypothyroidism versus those who remained euthyroid (26.7 ± 5.5 vs 24.9 ± 4.5 respectively, \(P = .10\)). Contrariwise, patients who developed overt thyrotoxicosis had significantly higher BMI compared to those remaining euthyroid (28.9 ± 5.9 vs 24.9 ± 4.5 respectively, \(P < .01\)). Of the 17 patients who developed overt thyrotoxicosis, 8 progressed to overt hypothyroidism (included in the thyroiditis category described below), 5 normalized their TSH, and 4 died within 3 months and long-term follow up was therefore unavailable.

Patients who developed subclinical (n = 4) or overt (n = 8) thyrotoxicosis followed by overt hypothyroidism were defined as thyroiditis (n = 12). Among those, 2 patients had a BMI <25, 6 patients ≥25-30, and 4 patient ≥30 kg/m². There was a significant correlation between

### Table 2. Predictors associated with any thyroid dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Any thyroid dysfunction (N = 72)</th>
<th>Euthyroid (N = 113)</th>
<th>Unadjusted OR (95% CI)</th>
<th>(P) value</th>
<th>Adjusted OR (95% CI)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.8 ± 13.0</td>
<td>62.8 ± 15.0</td>
<td>1.01 (0.99-1.03)</td>
<td>.35</td>
<td>1.01 (0.99-1.03)</td>
<td>.35</td>
</tr>
<tr>
<td>Male</td>
<td>52 (40.6)</td>
<td>76 (59.4)</td>
<td>1.27 (0.66-2.42)</td>
<td>.48</td>
<td>1.27 (0.66-2.42)</td>
<td>.48</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.0 ± 5.8</td>
<td>24.9 ± 4.5</td>
<td>1.09 (1.03-1.16)</td>
<td>&lt;.01</td>
<td>1.09 (1.02-1.16)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (44.8)</td>
<td>16 (55.2)</td>
<td>1.34 (0.60-2.97)</td>
<td>.48</td>
<td>1.34 (0.60-2.97)</td>
<td>.48</td>
</tr>
<tr>
<td>Malignancy</td>
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<tr>
<td>GI</td>
<td>14 (29.7)</td>
<td>33 (70.2)</td>
<td>1.22 (0.50-3.00)</td>
<td>0.66</td>
<td>1.22 (0.50-3.00)</td>
<td>0.66</td>
</tr>
<tr>
<td>GU</td>
<td>14 (33.3)</td>
<td>27 (65.9)</td>
<td>1.96 (0.93-4.11)</td>
<td>0.08</td>
<td>1.96 (0.93-4.11)</td>
<td>0.08</td>
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<tr>
<td>Lung</td>
<td>44 (45.3)</td>
<td>53 (54.6)</td>
<td>0.99 (0.92-1.06)</td>
<td>.71</td>
<td>0.99 (0.92-1.06)</td>
<td>.71</td>
</tr>
<tr>
<td>Time from diagnosis to ICI initiation, y</td>
<td>2.3 ± 4.1</td>
<td>2.6 ± 4.3</td>
<td>1.52 (1.13-2.40)</td>
<td>.01</td>
<td>1.52 (1.13-2.40)</td>
<td>.01</td>
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<tr>
<td>Tumor stage</td>
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<tr>
<td>III</td>
<td>30 (36.5)</td>
<td>52 (63.4)</td>
<td>1.17 (0.64-2.12)</td>
<td>0.62</td>
<td>1.17 (0.64-2.12)</td>
<td>0.62</td>
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<tr>
<td>IV</td>
<td>42 (40.8)</td>
<td>61 (59.8)</td>
<td>0.75 (0.39-1.40)</td>
<td>0.92</td>
<td>0.75 (0.39-1.40)</td>
<td>0.92</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>47 (36.4)</td>
<td>81 (63.3)</td>
<td>1.05 (0.41-2.71)</td>
<td>0.92</td>
<td>1.05 (0.41-2.71)</td>
<td>0.92</td>
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<tr>
<td>ICI type</td>
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<tr>
<td>PD-1</td>
<td>64 (38.8)</td>
<td>101 (61.2)</td>
<td>1.52 (1.13-2.40)</td>
<td>&lt;.01</td>
<td>1.52 (1.13-2.40)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>PD-L1</td>
<td>8 (40.0)</td>
<td>12 (60.0)</td>
<td>1.6 ± 0.9</td>
<td></td>
<td>1.6 ± 0.9</td>
<td></td>
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<tr>
<td>Baseline TSH, mU/L</td>
<td>2.0 ± 1.2</td>
<td>1.6 ± 0.9</td>
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</tbody>
</table>

Continuous parameters are shown as mean ± SD, and categorical variables as n (%) of the overall population.

Abbreviations: BMI, body mass index; GI, gastrointestinal; GU, genitourinary; ICI, immune checkpoint inhibitor; TSH, thyroid stimulating hormone; OR, odds ratio; CI, confidence interval.
BMI category and development of thyroiditis compared with the euthyroid group ($P = .01$).

**Time to development of overt hypothyroidism and overt thyrotoxicosis.** The time from first treatment with ICI to the development of overt hypothyroidism or overt thyrotoxicosis was stratified by BMI category. The median time to develop overt hypothyroidism was 58.5 (IQR 40.5-130) days and did not differ by BMI category. The median time to develop overt thyrotoxicosis was 31.0 (IQR 22.0-47.0) days and occurred significantly earlier in patients with higher BMI category (Figure 4). In patients with low-normal BMI, overt thyrotoxicosis occurred at a median of 57.5 (IQR 31.8-78.8) days versus 38.0 (IQR 26.8-40.5) days in the overweight category versus 23.0 (IQR 21.0-28.0) days in the obese category ($P = .02$).

### Table 3. Predictors associated with overt thyroid dysfunction

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Overt thyroid dysfunction (N = 41)</th>
<th>Euthyroid (N = 113)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P value</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.4 ± 10.9</td>
<td>62.8 ± 15.0</td>
<td>1.01 (0.99-1.04)</td>
<td>.31</td>
<td>1.01 (0.99-1.04)</td>
<td>.31</td>
</tr>
<tr>
<td>Male</td>
<td>28 (21.9)</td>
<td>76 (59.4)</td>
<td>1.05 (0.49-2.26)</td>
<td>.90</td>
<td>1.05 (0.49-2.26)</td>
<td>.90</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.3 ± 6.0 s</td>
<td>24.9 ± 4.5</td>
<td>1.10 (1.02-1.18)</td>
<td>.01</td>
<td>1.10 (1.02-1.18)</td>
<td>.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (31.0)</td>
<td>16 (55.2)</td>
<td>1.71 (0.69-4.23)</td>
<td>.25</td>
<td>1.71 (0.69-4.23)</td>
<td>.25</td>
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<td>Malignancy</td>
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<tr>
<td>GI</td>
<td>9 (19.1)</td>
<td>33 (70.2)</td>
<td>1</td>
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<tr>
<td>GU</td>
<td>7 (17.1)</td>
<td>27 (65.9)</td>
<td>.95 (.31-2.89)</td>
<td>.93</td>
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<td></td>
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<tr>
<td>Lung</td>
<td>25 (25.8)</td>
<td>53 (54.6)</td>
<td>1.73 (.72-4.16)</td>
<td>.22</td>
<td>1.73 (.72-4.16)</td>
<td>.22</td>
</tr>
<tr>
<td>Time from diagnosis to ICI initiation, y</td>
<td>1.6 ± 2.9</td>
<td>2.6 ± 4.3</td>
<td>0.91 (0.78-1.07)</td>
<td>.26</td>
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<td>Tumor stage</td>
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<tr>
<td>III</td>
<td>19 (23.1)</td>
<td>52 (63.4)</td>
<td>1</td>
<td></td>
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</tr>
<tr>
<td>IV</td>
<td>22 (21.6)</td>
<td>61 (59.8)</td>
<td>.87 (.39-1.94)</td>
<td>.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>29 (22.7)</td>
<td>81 (63.3)</td>
<td>1.41 (0.56-3.52)</td>
<td>.46</td>
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<td>ICI type</td>
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<tr>
<td>PD-1</td>
<td>35 (21.2)</td>
<td>101 (60.0)</td>
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<tr>
<td>PD-L1</td>
<td>6 (30.0)</td>
<td>12 (40.0)</td>
<td>1.59 (.57-4.44)</td>
<td>.38</td>
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<tr>
<td>Baseline TSH, mU/L</td>
<td>2.2 ± 1.2</td>
<td>1.6 ± 0.9</td>
<td>1.70 (1.14-2.52)</td>
<td>&lt;.01</td>
<td>1.70 (1.14-2.52)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Continuous parameters are shown as mean ± SD, and categorical variables as n (%) of the overall population. Abbreviations: BMI, body mass index; GI, gastrointestinal; GU, genitourinary; ICI, immune checkpoint inhibitor; TSH, thyroid stimulating hormone; OR, odds ratio; CI, confidence interval.

**Discussion**

This study assessed the impact of BMI on thyroid irAEs in a large cohort of patients with lung, GU, and GI cancer treated with PD-1 or PD-L1 inhibitors. Overall, 72 (38.9%) of patients developed any thyroid dysfunction, while 41 (22.1%) developed overt thyroid dysfunction, consistent with previously published real-world observational studies (12-15). Patients with higher BMI were at increased risk of developing any or
Overt thyroid dysfunction, such that for every 1 kg/m² increase in BMI, the risk of overt thyroid dysfunction increased by 10%. Specifically, overt thyrotoxicosis but not overt hypothyroidism was strongly associated with higher BMI.

The association between BMI, a surrogate measure of body fat, and immune function has been previously described. Obesity promotes a chronic state of inflammation, predisposing to both metabolic disorders and immune-mediated conditions. In obesity, visceral fat adipocytes secrete high levels of adipokines (leptin, adiponectin, resistin, visfatin) and cytokines (e.g., tumor necrosis factor-α, interleukin-6 and interleukin-1β) resulting in Th1/Th2 imbalance and promoting a pro-inflammatory state (31). The association between obesity and autoimmune thyroid disease has been demonstrated in a number of studies (32-34). Notably, a cross-sectional study demonstrated an increased prevalence of thyroid dysfunction and thyroid auto-antibodies among obese individuals, which correlated with increased leptin levels (32). It is likely that these pro-inflammatory factors similarly promote the development of thyroid irAE.

The relationship between high BMI and cancer outcomes is complex and was previously termed “the obesity paradox” (35). Thus, while high BMI increases the incidence, disease progression, recurrence, and mortality of some cancers, it is protective from other types of cancer. Furthermore, high BMI was reported to be associated with improved response to PD-1/PD-L1 inhibitors across cancer types (36-39). The underlying mechanism is not fully understood but is attributed at least in part to leptin regulation of T cell function (23). Studies in animal models and humans have demonstrated that obesity resulted in increased T cell exhaustion, characterized by decreased proliferative capacity and reduced interferon-γ and tumor necrosis factor-α production (23). This effect maybe a protective mechanism to counter the inflammatory state induced by obesity; however, in the context of cancer immune response, obesity was shown to increase the frequency of exhausted PD-1+CD8+ T cells both locally in the tumor microenvironment and systemically, resulting in accelerated tumor growth (23). Leptin was suggested to mediate the link between increased PD-1 expression on memory CD8+ T cells as it upregulates pSTAT3, an inducer of PD-1 expression in T cells through interaction with regulatory elements in the PD-1 gene promoter (40). Thus, PD-1-mediated T cell dysfunction in obesity resulted in increased responsiveness to immune checkpoint blockade. Of note, PD-1 expression in CD8+ T cells derived from obese ob/ob mice lacking leptin trended lower than in obese wild-type mice, suggesting that leptin contributes to PD-1 expression but is not required for it (23). Additional obesity related factors such as diet, genetics, and the gut microbiome are likely to play a role in cancer immune response in the context of immunotherapy.

The association between obesity and irAEs has been recently reported (41). In a multicenter, retrospective study, overweight and obese patients treated with PD-1 or PD-L1 inhibitors were more likely to develop irAEs affecting multiple organ systems. However, only overall endocrine irAEs were described, without differentiating the specific endocrine organ affected. An additional study investigated risk factors for irAEs in patients treated with PD-1 inhibitors and similarly found that higher BMI was associated with higher risk of irAEs; however, only 7 patients developed endocrine irAEs, the details of which are not reported (42). In our study, we focus specifically on thyroid irAEs and demonstrate the association of higher BMI with increased risk of thyroid dysfunction among a large cohort of patients, of whom 39% developed any thyroid dysfunction and 22% developed overt thyroid dysfunction. Our findings demonstrating a significantly higher incidence of thyroid irAEs in patients with higher BMI support the role of obesity in the complex interplay between inflammation and immune dysfunction in anti PD-1/L1 treated patients.

Interestingly, in our study overt thyrotoxicosis but not overt hypothyroidism was associated with increasing BMI. We speculate that this is most likely because overt thyrotoxicosis is representative of patients that developed immune-related thyroiditis, while those who developed hypothyroidism may be a more heterogeneous population including patients with background...
autoimmune thyroiditis and those who developed hypothyroidism as an incidental finding during follow-up. The diversity of this group is evidenced by the wide range of time to develop overt hypothyroidism. Unfortunately, Thyroid Peroxidase (TPO) antibodies were not available to further characterize this population.

Our study is the first to suggest that irAEs occur earlier in patients with higher BMI. Overt thyrotoxicosis occurred at a median of 3 weeks after treatment initiation in the obese group compared with a median of 5 weeks in the overweight group and 8 weeks in the euthyroid group. The earlier onset of overt thyrotoxicosis in the overweight and obese groups may be indicative of a more robust immune response in patients with higher BMI.

The strength of our study lies in our assessment of a large cohort of patients treated with PD-1 and PD-L1 inhibitors for various malignancies and for whom we have computerized access to their laboratory data and hospital clinic visits. These data have allowed us to analyze thyroid function parameters prior to and following ICI initiation. Several limitations of our study are noted. First, as in any retrospective study, there may be residual bias or confounders as patients presenting with symptoms consistent with thyroid dysfunction may have had more frequent thyroid function testing. Additionally, given that the study data were derived from a single institution in 1 geographic location, further studies are needed to verify whether the results can be extrapolated to other populations. Moreover, there were no prespecified intervals for TFT measurements. Second, we did not have access to additional parameters that may account for the treatment effect noted, such as TPO antibody status. Lastly, response to treatment was unreliablely recorded in our computerized database and therefore we were unable to assess the correlation among treatment response, BMI, and irAEs.

In conclusion, our data demonstrate that higher BMI is associated with increased risk of overt thyroid dysfunction in patients treated with PD-1 or PD-L1 inhibitors. Specifically, overt thyrotoxicosis but not hypothyroidism is strongly associated with BMI. Overt thyrotoxicosis occurred earlier in patients with higher BMI, suggesting a more robust immune response with increasing BMI. Further exploration of the interaction between obesity and immunotherapy may provide insight into the role of inflammation in mediating the immune response.

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Additional Information

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References


