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CASE REPORT

# Apalutamide-induced severe hypothyroidism: case series and practice recommendations for thyroid management

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## Abstract

The androgen receptor signaling inhibitor apalutamide is used successfully for the treatment of prostate cancer. An increased risk of hypothyroidism, mostly subclinical, has been reported in the SPARTAN and TITAN trials. We present three cases of subacute deterioration of previously known but well-controlled hypothyroidism treated with levothyroxine, occurring shortly after the initiation of treatment with apalutamide, resulting in severe hypothyroidism. These cases highlight the importance of awareness of thyroid dysfunction during treatment with apalutamide, particularly in patients with pre-existing thyroid disease, common in the general population. We provide practice recommendations for thyroid management prior to and during apalutamide treatment as well as after the interruption of this therapy.

Keywords: apalutamide; glucuronidation; hypothyroidism; levothyroxine; prostate cancer

## Established facts and novel insights

### Established Facts

- Increased risk of hypothyroidism has been reported in the SPARTAN and TITAN trials, investigating the androgen receptor signaling inhibitor apalutamide for the treatment of prostate cancer.

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## Novel Insights

- Starting treatment with apalutamide in patients with known but well-controlled hypothyroidism might result in severe hypothyroidism.
- When starting treatment with apalutamide, thyroid function tests must be checked regularly, especially in patients already treated with levothyroxine, and a dose increase must be anticipated.
- When apalutamide is interrupted, levothyroxine should be decreased to the pre-apalutamide dose.

## Introduction

Apalutamide is an androgen receptor signaling inhibitor which is increasingly used for the treatment of prostate cancer (PCa) (1). In the SPARTAN (2) and TITAN (3) trials, an increased risk of hypothyroidism was observed in the androgen-deprivation therapy (ADT) plus apalutamide-treated PCa group compared to the ADT plus placebo-treated group (respectively 8.1% vs 2.0% and 6.5% vs 1.1%). The risk was much higher in the subgroup treated with levothyroxine (L-T4) prior to inclusion (28% vs. 5.9%) (4). Hypothyroidism, mostly mild (subclinical) forms caused by chronic autoimmune thyroiditis, is very common, ranging from 4 to 9% of the elderly (5). Severe hypothyroidism, if left untreated, is associated with morbidity, such as fatigue, constipation, cognitive dysfunction, and fluid retention (5). We aim to present three cases of severe hypothyroidism under apalutamide and to formulate clinical practice recommendations to assist in thyroid management in apalutamide-treated PCa patients.

## Case presentations

### Patient 1

A 76-year-old man underwent a thyroidectomy for multinodular goiter 6 years earlier, followed by L-T4 supplementation. Five months later, he was diagnosed with PCa and underwent a radical prostatectomy (pT2aN0) and salvage radiotherapy on the pelvis and prostate. Nineteen months later, degarelix (a gonadotropin-releasing hormone (GnRH) antagonist) was initiated due to biochemical progression. During this treatment, serum levels of thyroid-stimulating hormone (TSH) and L-T4 dosage remained stable. Twenty-six months later, apalutamide was associated with progressive biochemical disease. As shown in Table 1 (upper part), after 2 months under apalutamide, he developed overt hypothyroidism (increased TSH up to 81.7 mIU/L and decreased free T4 (fT4)). The dosage of L-T4 was gradually increased up to +146% of the dosage prior to the initiation of apalutamide. Fourteen months later, apalutamide was stopped due to dermatological side effects (tibial wound). A preventive dose reduction of L-T4 was proposed back to the baseline dosage, after which he returned to normal serum TSH and fT4 levels.

### Patient 2

A 56-year-old man underwent total thyroidectomy for Graves' disease resistant to medical therapy and complicated with orbitopathy (thyroid eye disease), followed by L-T4 supplementation. Two years later, he was diagnosed with PCa (cT2aN0M0) for which he received radiotherapy with curative intent. At the age of 65 years, a rise in PSA levels led to the finding of lymph node metastases (pelvis and retroperitoneal), and he was started on triptorelin (GnRH agonist) and apalutamide. One month after the start of ADT, L-T4 supplementation was no longer adequate, with elevated TSH levels (37 mIU/L). The dosage of L-T4 was gradually increased by up to +82% of the dosage prior to the start of ADT until the normalization of TSH levels occurred (Table 1, middle part).

### Patient 3

A 64-year-old man was diagnosed with autoimmune hypothyroidism and was treated with L-T4, resulting in swift serum TSH normalization. Three years later, he was diagnosed with upfront lymph node- (pelvis and retroperitoneal) and bone-metastasized PCa for which combination treatment with degarelix and apalutamide was started. Two months later, he developed hypothyroidism (increased TSH up to 35.5 mIU/L), for which the dosage of L-T4 was gradually increased up to +80% of the dosage prior to the treatment, and a new steady state (serum TSH normalization) has not been reached yet (Table 1, lower part).

## Discussion

We describe three cases with subacute deterioration of previously known but well-controlled (under treatment with L-T4) hypothyroidism, occurring after the initiation of treatment with apalutamide, resulting in severe hypothyroidism. The first patient suffered from non-metastatic castration-resistant PCa, while the other two

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**Table 1** Evolution of thyroid function tests and treatment.

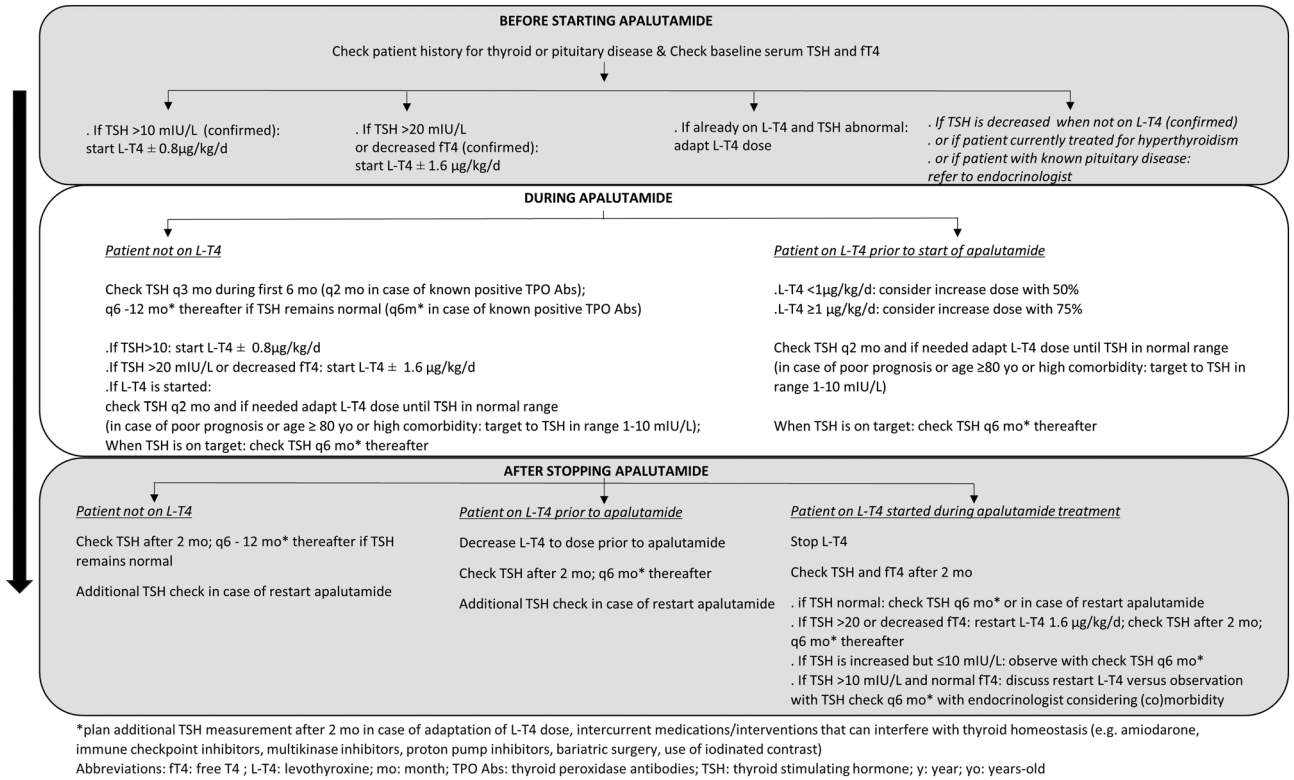
| Patient/timeline | TSH, mIU/L | fT4, pmol/L | L-T4, µg/day | ↑L-T4[b] |
|---|---|---|---|---|
| Patient 1 | | | | |
| 0 month | 0.25 | 22.8 | 162.5 | |
| Start apalutamide[a] at 0 month | | | | |
| +2 months | 49.8 | 10.8 | 162.5 | +0% |
| +4 months | 81.7 | | 175 | +8% |
| +5 months | 62.3 | | 225 | +38% |
| +7 months | 55.6 | 13.4 | 250 | +54% |
| +10 months | 73.3 | 10.1 | 275 | +69% |
| +11 months | 36.1 | 16.4 | 300 | +85% |
| +13 months | 32.2 | 17.8 | 400 | +146% |
| Stop apalutamide at +14 months | | | | |
| +15 months | 20.4 | 19.2 | 162.5 | +0% |
| +20 months | 1.02 | 21.8 | 162.5 | +0% |
| +23 months | 1.08 | 22.9 | 162.5 | +0% |
| Reference range | 0.27–4.2 | 12–22 | | |
| Patient 2 | | | | |
| −3 months | 0.29 | 13.3 | 137.5 | |
| 0 month | 0.43 | 12.2 | 137.5 | |
| Start triptorelin + apalutamide at 0 month | | | | |
| +1 month | 37.0 | 7.2 | 137.5 | +0% |
| +4 months | 32.0 | 7.2 | 164.3 | +19% |
| +7 months | 18.0 | 7.4 | 22 | +45% |
| +9 months | 6.8 | 9.2 | 225 | +64% |
| +10 months | 4.2 | 7.5 | 250 | +82% |
| Reference range | 0.38–5.3 | 7.0–16.0 | | |
| Patient 3 | | | | |
| −22 months | 2.0 | | 125 | |
| −4 months | 1.1 | | 125 | |
| Start degarelix + apalutamide at 0 month | | | | |
| +2 months | 35.5 | | 125 | +0% |
| +8 months | 24.8 | 20.0 | 150 | +20% |
| +10 months | 20.9 | 17.6 | 175 | +40% |
| +13 months | 13.4 | 22.3 | 200 | +60% |
| +16 months | 7.84 | 20.5 | 225 | +80% |
| Reference range | 0.27–4.2 | 11.9–21.6 | | |

[a]Degarelix since 10/2019; [b]% vs baseline.
fT4, free T4; L-T4, levothyroxine; TSH, thyroid-stimulating hormone; ↑, increase.

patients suffered from metastatic castration-sensitive PCa. Due to underlying thyroid disease, due to either prior thyroidectomy or end-stage autoimmune thyroiditis, all three patients had virtually no endogenous thyroid hormone production. Compliance and gastrointestinal function were normal, without concomitant intake of drugs or supplements that could interfere with gastrointestinal uptake or metabolism of L-T4.

Apalutamide is believed to induce hepatic glucuronidation of thyroid hormone by increasing the UDP glucuronyltransferase (4). However, more research is needed to confirm this hypothesis as well as to exclude other possible modes of actions such as, for example, increase in thyroid-binding globulin, effects on other metabolizing enzymes such as deiodinases, or thyroid auto-immunity. In normal circumstances, decreased fT4 leads to increased TSH secretion, resulting in increased thyroid hormone production. Here, failure of thyroidal compensation results in consumptive hypothyroidism as is also observed with other drugs such as the anti-epileptic drug valproic acid and multikinase inhibitors.

In all three cases, a severely increased serum TSH (>30 mIU/L) was observed already after 1 to 2 months under apalutamide treatment, thus much earlier than the median time to first TSH rise in SPARTAN of 113 days (2), with a need to double the L-T4 dosage. Vice versa, the L-T4 needs to return to baseline after stopping apalutamide, as observed in patient 1, underlining the importance of anticipation with a swift reduction to




*plan additional TSH measurement after 2 mo in case of adaptation of L-T4 dose, intercurrent medications/interventions that can interfere with thyroid homeostasis (e.g. amiodarone, immune checkpoint inhibitors, multikinase inhibitors, proton pump inhibitors, bariatric surgery, use of iodinated contrast)
Abbreviations: fT4: free T4 ; L-T4: levothyroxine; mo: month; TPO Abs: thyroid peroxidase antibodies; TSH: thyroid stimulating hormone; y: year; yo: years-old

**Figure 1**

Practice recommendations for thyroid management in apalutamide-treated prostate cancer patients.

the pre-apalutamide L-T4 dosage when apalutamide is temporarily or definitively stopped.

Based on the available data from the trials and case reports (6, 7) and in view of the increasing use of apalutamide worldwide (1), in Fig. 1, we provide practice recommendations for thyroid management prior to and during apalutamide, as well as after the interruption of apalutamide. These practice recommendations are based on our own clinical experience and are compatible with current recommendations for the management of hypothyroidism (8, 9). Close collaboration with the general practitioner, uro-oncologist, and endocrinologist is mandatory in cases of known thyroid disease (hypothyroidism, hyperthyroidism, and thyroid cancer), pituitary disease, severe gastrointestinal malabsorption (e.g. post-bariatric surgery), or concomitant treatment with anti-cancer therapies or other drugs known to interfere with thyroid hormone homeostasis (e.g. immune checkpoint inhibitors and multikinase inhibitors). Thyroid dysfunction does not represent a contraindication to start or continue apalutamide. When L-T4 is started or increased in PCa patients with poor prognosis, age ≥80 years, or high comorbidity, a serum TSH between 1 and 10 mIU/L should be targeted rather than a TSH within the laboratory reference range, as suggested by the guidelines (8, 9).

Awaiting long-term data from the pivotal trials, real-world data are needed regarding the impact of apalutamide and other potent androgen receptor pathway inhibitors on thyroid hormone homeostasis. More insight is needed into the hormonal and possible anti-tumoral effects of thyroid hormonal changes induced by apalutamide in PCa patients. In the meantime, awareness of the risk of and clinical guidance on apalutamide-induced thyroid dysfunction is of utmost importance in the highly vulnerable patient population with advanced PCa.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of these case series and practice recommendations.

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**Statement of ethics**

This study was approved by the Ethics Committee of the University Hospitals Leuven.

**Patient consent**
Written informed consent for publication of their clinical details was obtained from the patients.

**Author contribution statement**
KD and BD drafted the manuscript, and PVC, AMVdB, FD, FC, AG, and SJ reviewed it critically.

## References

1 EAU Guidelines. Edn presented at the EAU Annual Congress Paris 2024. Arnhem, The Netherlands. ISBN 978-94-92671-23-3 2024. Available at: https://uroweb.org/guidelines.

2 Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, Olmos D, Mainwaring PN, Lee JY, Uemura H, *et al.* Apalutamide treatment and metastasis-free survival in prostate cancer. *New England Journal of Medicine* 2018 **378** 1408–1418. (https://doi.org/10.1056/NEJMoa1715546)

3 Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, Juárez Soto Á, Merseburger AS, Özgüroğlu M, Uemura H, *et al.* Apalutamide for metastatic, castration-sensitive prostate cancer. *New England Journal of Medicine* 2019 **381** 13–24. (https://doi.org/10.1056/NEJMoa1903307)

4 Available at: https://ec.europa.eu/health/documents/community-register/2019/20190114143258/anx_143258_en.pdf.

5 Chaker L, Razvi S, Bensenor IM, Azizi F, Pearce EN & Peeters RP. Hypothyroidism. *Nature Reviews. Disease Primers* 2022 **8** 30. (https://doi.org/10.1038/s41572-022-00357-7)

6 Daviduck Q, North S & Swaleh R. Hypothyroidism caused by apalutamide. *CMAJ* 2023 **195** E1443. (https://doi.org/10.1503/cmaj.230555)

7 Moffatt C, Lechner MG, Angell TE, Shen J, Drakaki A, Acosta GJ, Liang TZ & Tsai K. The effect of apalutamide on thyroid function in prostate cancer patients. *Journal of the Endocrine Society* 2024 **8** bvae105. (https://doi.org/10.1210/jendso/bvae105)

8 Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S & Wemeau JL. 2013 ETA guideline: management of subclinical hypothyroidism. *European Thyroid Journal* 2013 **2** 215–228. (https://doi.org/10.1159/000356507)

9 Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS, *et al.* Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. *Thyroid* 2014 **24** 1670–1751. (https://doi.org/10.1089/thy.2014.0028)