

# Symptoms of hypogonadism caused by 5 $\alpha$ -reductase inhibitors

## Abstract

Hypogonadism causes libido loss, body hair loss, mood depression, muscle volume reduction, and hot flashes. These symptoms can be due to lack of testosterone secretion from the testes or of testosterone action in target organs. 5 $\alpha$ -reductase inhibitors (5-ARIs), often contained in hair growth-promoting agent, are known not to cause hypogonadism because they reduce dihydrotestosterone and do not decrease total testosterone (TT). We here report a patient with strong cold sensation and paresthesia of lower extremities and hypogonadism caused by 5-ARIs taken orally. A 28-year-old man visited our hospital with fatigue and strong cold sensation and paresthesia of lower extremities. He was taking 2 tablet-types of 5-ARIs. The one was finasteride (1mg/day), an imported medicine for personal use, and the other was saw palmetto (fruit extract 320mg/day), an over-the-counter drug in Japan. Laboratory testing revealed TT, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels of 160 ng/dL, 2.4mIU/mL and 8.4mIU/mL, respectively. We diagnosed hypogonadism due to a lack of testosterone secretion. Eight days after discontinuing both drugs, TT, FSH and LH levels improved to 404ng/dL, 2.3mIU/mL and 5.1 mIU/mL, and his symptoms improved completely in a month. Physicians should consider 5-ARIs as a cause of cold sensation and paresthesia of lower extremities and carefully check every ingested drug including imported and over-the-counter drugs.

**Keywords:** 5 $\alpha$ -reductase inhibitors(5-ARIs), cold sensation, dihydrotestosterone, dutasteride, finasteride, hypogonadism, over-the-counter drugs, paresthesia of lower extremities, saw palmetto, testosterone

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**Abbreviations:** 5-ARIs, 5 $\alpha$ -reductase inhibitors; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TT, total testosterone

## Introduction

Hypogonadism is a disease to cause decreased energy, libido loss, body hair loss, mood depression, muscle volume reduction, and hot flashes.<sup>1-3</sup> 5 $\alpha$ -reductase inhibitors (5-ARIs) are administered orally for male pattern alopecia and benign prostatic hyperplasia due to decrease of dihydrotestosterone, a potent male hormone.<sup>4</sup> 5-ARIs are generally known not to cause hypogonadism because 5-ARIs do not decrease total testosterone (TT);<sup>4-8</sup> decreased testosterone causes hypogonadism. In recent years, 2 reports suggested that 5-ARIs may decrease TT to cause symptoms of hypogonadism,<sup>9,10</sup> but there is no report that 5-ARIs caused cold sensation and paresthesia of lower extremities. We here report a patient with strong cold sensation and paresthesia of lower extremities and symptoms of hypogonadism due to 2 types of oral 5-ARIs. The one was finasteride, an imported medicine for personal use, and the other was saw palmetto, an over-the-counter drug in Japan.

## Case presentation

A 28-year-old previously healthy man visited our hospital with strong cold sensation and paresthesia of lower extremities for 3 months, and additional symptoms included palpitations, headache, and fatigue. He had been taking 2 tablet-types of 5-ARIs (finasteride (1mg/day) and saw palmetto (fruit extract 320mg/day)) for alopecia prevention in the 4 months before his visit. On physical examination, we found no abnormalities in his thyroid gland and limbs. Laboratory testing revealed TT, follicle-stimulating hormone (FSH), and

luteinizing hormone (LH) levels of 160ng/dL, 2.4mIU/mL, 8.4mIU/mL, respectively. TT was under the lower end of the range for his age. We diagnosed him with hypogonadism due to a lack of testosterone secretion. Eight days after he stopped taking both drugs, TT, FSH and LH levels improved to 404ng/dL, 2.3mIU/mL and 5.1mIU/mL, respectively. After a month, all symptoms were completely resolved.

## Discussion

From our patient, we have learned the following: 5-ARIs can cause symptoms of hypogonadism. 5-ARIs can cause cold sensation and paresthesia of lower extremities. Medical professionals should review every drug as a potential source of symptoms. Firstly, 5-ARIs can cause symptoms of hypogonadism. In general, primary hypogonadism that develops after puberty is diagnosed by both decreases in TT value and its consistent symptoms;<sup>2</sup> however, it may be under diagnosed due to 2 reasons. First, signs and symptoms of hypogonadism are often unspecific.<sup>1</sup> Second, TT value should be evaluated considering the patient's age. According to general guidelines, the cut-off value of TT is around 200 to 300ng/dL,<sup>1-12</sup> although the reference value is relatively higher in some young people.<sup>13</sup> 5-ARIs are known not to decrease TT. Only two reports have shown that 5-ARIs (finasteride, dutasteride) statistically reduced TT.<sup>9,10</sup> One report suggested that 5-ARIs (dutasteride) tended to reduce TT,<sup>14</sup> but it is statistically not significant. Although pharmacological and biochemical mechanisms of decreased TT by 5-ARIs are unknown, we thought that some ingredients (e.g., excipients of tablets, tiny amount of other component except finasteride and saw palmetto) contained in both tablets might have affected the cascade of sex hormone metabolism or a paradoxical reaction happened in the patient.

Also, saw palmetto might accelerate some interaction with finasteride by inhibiting 5 $\alpha$ -reductase.<sup>15,16</sup> Saw palmetto is widely used as herbal preparations for the treatment of benign prostatic hyperplasia or alopecia. The berries of saw palmetto consist of fatty acids, phytosterols (e.g.,  $\beta$ -sitosterol, stigmasterol) and fatty alcohols.<sup>17,18</sup> The mechanisms of pharmacological action of saw palmetto were not fully understood, although numerous proposals have been made, including inhibition of 5ARIs.<sup>18</sup> Secondly, 5-ARIs can cause cold sensation and paresthesia of lower extremities. The patient complained of strong cold sensation and paresthesia of lower extremities as his main symptom, unlike ordinary hypogonadism or low TT level.<sup>1-3</sup> We first excluded peripheral arterial disease and endocrine disorders (common diseases such as hypothyroidism). After that, we diagnosed that 5-ARIs were responsible for his symptoms based on the following 3 points:<sup>17</sup>

- I. His symptoms occurred for the first time after taking 5-ARIs;
- II. His symptoms and laboratory findings improved promptly after discontinuing 5-ARIs;
- III. No other diseases were identified. However, it remains unclear whether the symptoms of the patient were due to the combination or to either of the two drugs.

Finally, physicians should review all patients' drugs, including imported, over-the-counter, supplemental, and folk drugs. Patients don't usually share all their medications and issues (especially sexual performance or personal appearance), especially if confidential relationships between them are not fully established.<sup>20</sup> In Japan, finasteride is available only on prescription from the Japanese national public medical insurance and not as an over-the-counter drug. However, many people import finasteride because it is expensive in this country. Saw palmetto is available as an over-the-counter supplement for benign prostatic hyperplasia and male pattern alopecia. Increased use of imported and over-the-counter drugs would increase the number of side effects. Physicians should consider 5-ARIs as a cause of cold sensation and paresthesia of lower extremities and primary hypogonadism and carefully review every ingested drug including imported and over-the-counter medications.

## Patient consent form

Written informed consent for patient information to be published was provided by the patient.

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## Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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