

Transient Marked Increase in Serum Prostate-Specific Antigen Level with Increased Libido Following Testosterone Enanthate Injection in a Depressed Man with Late-Onset Hypogonadism

Shoko Kimura, MD, Nobukazu Sasaki, MD, Yuji Aoki, MD, PhD*

Department of Internal Medicine, National Hospital Organization Matsumoto Medical Center, Matsumoto, Japan

*Corresponding author: Yuji Aoki

| Received: 12.02.2019 | Accepted: 22.02.2019 | Published: 28.02.2019

DOI: 10.36347/sjmcr.2019.v07i02.016

Abstract

Case Report

Depression is a major health problem with increased morbidity and decreased quality of life. Symptoms of depressed men overlap with those of men with late-onset hypogonadism (LOH). The present case of a 66-year-old man had been treated for depression at a psychiatric hospital for six years, after experiencing a serious event in his life. During the course, he developed type 2 diabetes and hyponatremia. A few days after most psychotropic drugs were discontinued considering possible adverse effects, the patient was transferred to our hospital due to treatment-resistant depression. His glycemic control remained good (HbA1c, 6.3 %). His hyponatremia (126 mEq/L) was gradually improved, but his depressive symptoms persisted. Thereafter, he was diagnosed with LOH and benign prostatic hyperplasia, and 125 mg testosterone enanthate was injected. Shortly after the injection, a transient but marked increase in serum prostate-specific antigen levels from 0.9 to 32.3 ng/mL was found. In parallel, the patient's libido was unnecessarily increased in addition to the improvement of his depressive mood. Thus, some favorable and unfavorable effects of testosterone supplementation were observed in the present case. Although testosterone replacement therapy is expected to be effective for LOH, more accurate diagnosis, more favorable management and more careful monitoring would be required.

Keywords: Late-onset hypogonadism, depression, testosterone enanthate, prostate-specific antigen, libido.

Copyright © 2019: This is an open-access article distributed under the terms of the Creative Commons Attribution license which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use (NonCommercial, or CC-BY-NC) provided the original author and source are credited.

INTRODUCTION

Depression is a major health problem with increased morbidity and decreased quality of life, especially in the elderly population [1, 2]. Some depressed men have low testosterone levels [3-5], and symptoms of depressed men overlap with those of men with late-onset hypogonadism (LOH), which is regarded as a clinical and biochemical state characterized by particular symptoms (fatigue, decreased libido, memory problems, etc.) and a low level of serum testosterone with advancing age [6, 7]. Causal relationships between hypogonadism and depression are inconclusive and seem to be bidirectional [8-10]. A systematic review demonstrated significant antidepressant effects of testosterone supplementation in depressed patients with hypogonadism or acquired immunodeficiency syndrome as well as in patients treated with testosterone gel [11].

Testosterone replacement therapy in elderly men is expected to have beneficial effects on sexual function, mood and quality of life, but a careful

monitoring of potential adverse effects such as changes of the biology of the prostate is necessary [12]. In the present case, a transient but marked increase in serum prostate-specific antigen (PSA) levels with unnecessarily increased libido was observed following the testosterone supplementation.

CASE REPORT

A 66-year-old man with type 2 diabetes and hyponatremia was transferred from a psychiatric hospital to our hospital due to treatment-resistant depression. He had been treated for depression at the psychiatric hospital for six years, after experiencing a serious event in his life. During the course, he developed type 2 diabetes and hyponatremia. His hyponatremia was suspected to be associated with psychotropic drugs. The syndrome of inappropriate secretion of antidiuretic hormone was interpreted negatively, because his plasma antidiuretic hormone level was previously detected at less than 0.4 pg/mL when the serum sodium level was 124 mEq/L. A few days before his admission, 20 mg of escitalopram (a selective serotonin reuptake inhibitor), 37.5 mg of

venlafaxine (a serotonin-norepinephrine reuptake inhibitor) and 8 mg of perospirone (a serotonin-dopamine antagonist) were discontinued, and he continued to take only benzodiazepines (1 mg of lorazepam and 5 mg of nitrazepam).

On admission, the patient was 156 cm in height and 56.3 kg in weight. The patient's white blood cell count was 9,760/ μ L, hemoglobin was 13.2 g/dL, and platelet count was 219,000/ μ L. The levels of serum total protein, albumin, urea nitrogen, creatinine, sodium, potassium and C-reactive protein were 5.8 g/dL, 3.6 g/dL, 11 mg/dL, 0.68 mg/dL, 126 mEq/L, 3.5 mEq/L and 1.15 mg/dL, respectively. His glycemic control was good at the HbA1c level of 6.3 % under the treatment with 40 mg of gliclazide (a sulfonylurea) and 75 mg of sitagliptin (a dipeptidyl peptidase-4 inhibitor). Consulting a psychiatrist, 1 mg of lorazepam was also discontinued 5 days after admission. Due to some difficulty in urination, the patient was diagnosed with mild benign prostatic hyperplasia (approximately 4 cm in diameter) by a urologist. The treatment with 8 mg of silodosin (an α 1-adrenoreceptor antagonist) was started on day 15 in the hospital, and then it was switched to that with 0.5 mg of dutasteride (a 5 α -reductase inhibitor) on day 37. With the discontinuation of the psychotropic drugs and without salt restriction, the

serum sodium level increased to 133 mEq/L on day 43, but his depressive symptoms persisted.

As shown in Table 1, his serum levels of luteinizing hormone and free testosterone on day 19 were found to be 15.81 mIU/mL and 4.1 pg/mL, respectively, suggesting LOH. Therefore, 125 mg of testosterone enanthate was injected intramuscularly on day 45. After the testosterone supplementation, his depressive mood and activity tended to be improved, but the increased libido perplexed a few female members of the medical staff. Surprisingly, it was found that the patient's serum PSA levels were markedly increased from 0.894 to 32.313 ng/mL twelve days after the injection of testosterone. Thirty-three days after the injection, the serum PSA level decreased to 3.822 ng/mL within the normal range. At that time his serum free testosterone level, the assay of which had little cross-reactivity with testosterone enanthate, was increased to 6.8 pg/mL within the normal range, implying functional hypogonadism. Changes in the luteinizing hormone levels indicated the bioactivity of the testosterone enanthate injection. Since his depressive symptoms were moderately improved, he returned to the psychiatric hospital under the treatment with 40 mg of gliclazide, 5 mg of nitrazepam and 0.5 mg of dutasteride.

Table-1: Changes in the patient's laboratory data in the hospital

Serum levels of	Day 19	Day 57	Day 78	Reference range
Albumin	3.5	3.2	3.5	4.1-5.1 g/dL
Sodium	130	135	132	138-145 mM/L
Potassium	3.9	3.6	3.8	3.6-4.8 mM/L
Luteinizing hormone	15.81	1.68	8.63	0.79-5.72 mIU/mL
Free testosterone	4.1	4.9	6.8	5.3-11.5 pg/mL
PSA	0.894	32.313	3.822	0-4 ng/mL

Testosterone enanthate (125 mg), with little cross-reactivity in the assay of serum free testosterone level, was injected intramuscularly on day 45 in the hospital. PSA, prostate-specific antigen

DISCUSSION

In the present patient with treatment-resistant depression, testosterone supplementation showed some beneficial effects on depressive symptoms, as indicated in the previous reports [11, 13-15]. The patient's decreased free testosterone and increased luteinizing hormone levels imply primary hypogonadism [16, 17], and from his clinical course it is inferred that he had functional hypogonadism or LOH associated with depression and/or psychotropic drugs prescribed [18], without using stringent criteria for LOH [19]. LOH has been documented in patients with type 2 diabetes [16, 17, 20], but this seems not to be applicable for the present case in view of his non-obese and well-controlled diabetes [18, 19].

It is of note that the testosterone supplementation caused a transient but marked increase in the serum PSA levels from 0.9 to 32.3 ng/mL. Thus

far, to our best knowledge, no reports have demonstrated such a marked increase of serum PSA level following testosterone supplementation. In the previous reports [21-24], serum PSA levels shortly after the first testosterone supplementation, as seen in the present patient, were not shown (or measured). The intramuscular injection of testosterone enanthate (125 mg) as testosterone supplementation, which is only permitted by health insurance medical treatment in Japan at present, may be not appropriate for an initial treatment of LOH, compared with topical testosterone gel [19], particularly for the patient with benign prostatic hyperplasia. However, there is a report that 250 mg of testosterone enanthate every 4 weeks could improve lower urinary tract symptoms at the 12-month visit in patients with hypogonadism and benign prostatic hyperplasia [25]. A recent review also demonstrated the safety and efficacy of testosterone

supplementation in common prostatic conditions including benign prostatic hyperplasia [26].

Another notable point is that the patient's libido was unnecessarily increased following the one-time testosterone supplementation. In parallel, the patient's depressive mood was moderately improved, and such improvement lasted until discharge while receiving a 5 α -reductase inhibitor (antiandrogen) for benign prostatic hyperplasia by a urologist's discretion. Although 5 α -reductase inhibitors appear to work against testosterone supplementation, such counteraction is thought to occur in the prostate but not in psychosexual behavior [27], probably leading to rather favorable interactions.

CONCLUSION

It is thus demonstrated in the present case report that some favorable and unfavorable effects of testosterone supplementation were exerted shortly after the injection of testosterone enanthate only once in a depressed man with LOH and benign prostatic hyperplasia. Although testosterone supplementation is expected to be effective for LOH, more accurate diagnosis, more favorable management and more careful monitoring would be required.

Conflict of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

REFERENCES

- Unützer J. Clinical practice. Late-life depression. *N Engl J Med*. 2007; 357(22): 2269-2276.
- Damme AV, Declercq T, Lemey L, Tandt H, Petrovic M. Late-life depression: issues for the general practitioner. *Int J Gen Med*. 2018; 11: 113-120.
- Seidman SN, Walsh BT. Testosterone and depression in aging men. *Am J Geriatr Psychiatry*. 1999; 7(1): 18-33.
- Shores MM, Sloan KL, Matsumoto AM, Moceri VM, Felker B, Kivlahan DR. Increased incidence of diagnosed depressive illness in hypogonadal older men. *Arch Gen Psychiatry*. 2004; 61(2): 162-167.
- Kheirkhah F, Hosseini SR, Hosseini SF, Ghasemi N, Bijani A, Cumming RG. Relationship between testosterone levels and depressive symptoms in older men in Amirkola, Iran. *Caspian J Intern Med*. 2014; 5(2): 65-70.
- Wu FCW, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Lean MEJ, Pendleton N, Punab M, Boonen S, Vanderschueren D, Labrie F, Huhtaniemi I. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med*. 2010; 363 (2): 123-135.
- Singh P. Andropause: current concepts. *Indian J Endocrinol Metab*. 2013; 17 (Suppl 3): S621-S629.
- Margolese HC. The male menopause and mood: testosterone decline and depression in the aging male – is there a link? *J Geriatr Psychiatry Neurol*. 2000; 13(2): 93-101.
- Almeida OP, Yeap BB, Hankey GJ, Jamrozik K, Flicker L. Low free testosterone concentration as a potentially treatable cause of depressive symptoms in older men. *Arch Gen Psychiatry*. 2008; 65: 283-289.
- Kische H, Gross S, Wallaschofski H, Grabe HJ, Volzke H, Nauck M, Haring R. Associations of androgens with depressive symptoms and cognitive status in the general population. *PLOS ONE*. 2017; 12(5): e0177272.
- Zarrouf FA, Artz S, Griffith J, Sirbu C, Komor M. Testosterone and depression: systematic review and meta-analysis. *J Psychiatr Pract*. 2009; 15(4): 289-305.
- Nigro N, Christ-Crain M. Testosterone treatment in the aging male: myth or reality? *Swiss Med Wkly*. 2012; 142: w13539.
- Seidman SN, Rabkin JG. Testosterone replacement therapy for hypogonadal men with SSRI-refractory depression. *J Affect Disord*. 1998; 48(2-3): 157-161.
- Pope HG Jr, Cohane GH, Kanayama G, Siegel AJ, Hudson JI. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry*. 2003; 160(1): 105-111.
- Amanatkar HR, Chibnall JT, Seo BW, Manepalli JN, Grossberg GT. Impact of exogenous testosterone on mood: a systematic review and meta-analysis of randomized placebo-controlled trials. *Ann Clin Psychiatry*. 2014; 26(1): 19-32.
- Kapoor D, Aldred H, Clark S, Channer KS, Jones TH. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. *Diabetes Care*. 2007; 30: 911-917.
- Li Y, Zhang M, Liu X, Cui W, Rampersad S, Li F, Lin Z, Yang P, Li H, Sheng C, Cheng X, Qu S. Correlates and prevalence of hypogonadism in patients with early- and late-onset type 2 diabetes. *Andrology*. 2017; 5(4):739-743.
- Grossmann M, Matsumoto AM. A perspective on middle-aged and older men with functional hypogonadism: focus on holistic management. *J Clin Endocrinol Metab*. 2017; 102(3): 1067-1075.
- Livingston M, Kalansooriya A, Hartland AJ, Ramachandran S, Heald A. Serum testosterone levels in male hypogonadism: why and when to check – a review. *Int J Clin Pract* 2017; 71(11): e12995.
- Hackett G. Type 2 diabetes and testosterone therapy. *World J Mens Health* 2019; 37 (1): 31-44.
- Grober ED, Lamb DJ, Khera M, Murthy L,

- Lipshultz LI. Correlation between simultaneous PSA and serum testosterone concentrations among eugonadal, untreated hypogonadal and hypogonadal men receiving testosterone replacement therapy. *Int J Impot Res.* 2008; 20(6): 561-565.
22. Coward RM, Simhan J, Carson CC 3rd. Prostate-specific antigen changes and prostate cancer in hypogonadal men treated with testosterone replacement therapy. *BJU Int.* 2009; 103(9): 1179-1183.
23. Morgentaler A, Benesh JA, Denes BS, Kan-Dobrosky N, Harb D, Miller MG. Factors influencing prostate-specific antigen response among men treated with testosterone therapy for 6 months. *J Sex Med.* 2014; 11(11): 2818-2825.
24. Kato Y, Shigehara K, Nakashima K, Iijima M, Kawagushi S, Nohara T, Izumi K, Kadono Y, Konaka H, Namiki M, Mizokami A. The five-year effects of testosterone replacement therapy on lipid profile and glucose tolerance among hypogonadal men in Japan: a case control study. *Aging Male.* 2019; Jan 16: 1-6.
25. Shigehara K, Sugimoto K, Konaka H, Iijima M, Fukushima M, Maeda Y, Mizokami A, Koh E, Origasa H, Iwamoto T, Namiki M. Androgen replacement therapy contributes to improving lower urinary tract symptoms in patients with hypogonadism and benign prostate hypertrophy: a randomized controlled study. *Aging Male.* 2011; 14(1): 53-58.
26. Herati AS, Kohn TP, Butler PR, Lipshultz LI. Effects of testosterone on benign and malignant conditions of the prostate. *Curr Sex Health Rep.* 2017; 9(2): 65-73.
27. Randall VA. Role of 5 alpha-reductase in health and disease. *Baillieres Clin Endocrinol Metab.* 1994; 8(2): 405-431.