Original Article

The Prostate Saturation Point after Testosterone Replacement Therapy in Testosterone Deficiency Patient

Natdanai Sakonponwasin MD[1], Kun Sirisopana MD[1], Chinnakhet Ketsuwan MD[1], Wisoot Khongcharoensombat MD[1], Charoen Leenanupunth MD[1], Premsant Sangkum MD[1]

[1] Division of Urology, Department of Surgery, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Background: The effect of testosterone on the prostate gland is an unresolved question. The prostate saturation model is a recent hypothesis explaining that the stimulation of prostate tissue by testosterone is limited to a certain level of testosterone due to the limited number of androgen receptors. However, data from the Thai patients related to this issue are still lacking and need to be explored.

Objective: To investigate prostate changes after testosterone replacement therapy (TRT).

Materials and Methods: A retrospective study including testosterone-deficient patients who had TRT between 2011 and 2017 at Ramathibodi Hospital was conducted. The change in prostate-specific antigen (PSA) levels before and after TRT, or after a 1-year observation, was measured and analyzed as the primary objective. As a secondary objective, the authors measured and evaluated normal PSA velocity (PSAV) in the patients after TRT.

Results: One hundred eleven testosterone deficient patients were included for analysis. The mean age was 62 years old. The baseline testosterone level and PSA level at the beginning were 247 ng/dL and 1.16 ng/mL, respectively. After undergoing TRT for one year, the results showed that the testosterone and the PSA levels were 307 ng/dL and 1.46 ng/mL, respectively. In addition, the subgroup analysis illustrated that patients who had low baseline testosterone levels such as 247 ng/dL or less, had significant increase of PSA level after treatment. However, when the baseline testosterone level was more than 247 ng/dL, the PSA levels were steady after treatment. For the secondary-objective results, the PSAV of the testosterone deficiency patients after TRT was 0.3 ng/mL/year.

Conclusion: The evidence clearly indicates that TRT significantly increased the serum testosterone level. However, it had a limited effect on PSA change. The present study results supported the hypothesis of the prostate saturation model. The authors believe that a testosterone level of 247 ng/dL can saturate all androgen receptors in the prostate gland and no longer increase prostate stimulation.

Keywords: Prostate-specific antigen; Prostate cancer; Testosterone replacement Therapy; Prostate saturation

Received 16 February 2021 | Revised 7 April 2021 | Accepted 20 April 2021

J Med Assoc Thai 2021;104(9):1465-70

Website: http://www.jmatonline.com

Testosterone replacement therapy (TRT) can improve testosterone deficiency symptoms including erectile dysfunction, fatigue, depression, and loss of libido and muscle mass[1-4]. In addition, TRT can also help to improve the symptoms of metabolic syndrome. However, there is still a contraindication of TRT for the case of prostate cancer (PCa), despite large meta-analyses indicating that testosterone does not cause PCa or PCa progression[5-7]. In testosterone-deficient patients, the prostate-specific antigen (PSA) is recommended to be used for monitoring prostate changes during TRT, however it may be one confounding factor to PCa screening and early detection[8-10].

Old clinical trials in men with normal testosterone levels who received TRT indicated that an increase in testosterone to supraphysiologic levels did not affect PSA[11,12]. A study in PCa patients also showed that TRT could increase testosterone to physiologic level but there was no change in PSA or prostate cancer progression. This can be explained by the prostate saturation hypothesis[13].

Testosterone directly stimulates androgen receptors and regulates the gene for PSA. The effect of testosterone on the prostate gland is an unresolved question. The prostate saturation model is a recent hypothesis explaining that the stimulation of prostate tissue from testosterone is limited to a certain level of testosterone due to the limited number of androgen

Correspondence to:

Sangkum P.

Division of Urology, Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Toong Phayathai, Ratchathewi, Bangkok 10400, Thailand.

Phone: +66-2-2011315, **Fax**: +66-2-2794704

Email: premsanti@gmail.com

How to cite this article:

Sakonponwasin N, Sirisopana K, Ketsuwan C, Khongcharoensombat W, Leenanupund C, Sangkum P. The Prostate Saturation Point after Testosterone Replacement Therapy in Testosterone Deficiency Patient. J Med Assoc Thai 2021;104:1465-70.

doi.org/10.35755/jmedassocthai.2021.09.12630

receptors. Furthermore, the prostate saturation theory suggests that PSA and prostate tissue growth are sensitive to changes only when serum testosterone levels are low, when the amount of testosterone is not high enough to fully bind to all androgen receptors. In the present case, the prostate shrinks, and PSA levels decrease in hypogonadal men. Conversely, when testosterone serum levels increase to normal levels, all available androgen receptors are saturated by the testosterone. Consequently, further increases in the serum testosterone level have no effect on prostate size or PSA[13-15]. This is one of the most relevant hypotheses for explaining the correlation between TRT and prostate changes nowadays.

However, the data in Thai and other Asian populations related to the above-mentioned issue are still lacking and need to be explored. Therefore, the aim of the present study was to determine the testosterone levels that cause saturation in the prostate gland and prove the applicability of the prostate saturation model in Asian populations.

Materials and Methods

The study was conducted in agreement with the ethical principles of the Declaration of Helsinki and ethical approval for the research was permitted from the Institutional Review Board of the Faculty of Medicine, Ramathibodi Hospital (COA. No. MURA 2018/962). The present research was conducted as a retrospective study including testosterone-deficient patients who received TRT between 2011 and 2017 at the Urological Division, Ramathibodi Hospital, Thailand. The patients were treated with oral testosterone undecanoate, or testosterone transdermal gel, or testosterone undecanoate injection based on patient preference and all included patients must have had at least one year of follow-up after TRT.

One hundred forty-five patients received TRT during the present study period. However, only 111 patients were included for analysis, as shown in Figure 1, while 34 patients were excluded due to one of the exclusion criteria. These criteria were being suspected of having PCa from abnormal digital rectal examination, having a baseline PSA before starting TRT of more than 4 ng/mL, or having received 5-alpha reductase inhibitors (5ARI).

The primary objectives of the present study were to prove the prostate saturation model hypothesis, to identify the testosterone levels that caused saturation of androgen receptors in the prostate gland, and to explain the changes in the prostate gland by measuring PSA before and after TRT. The secondary objective

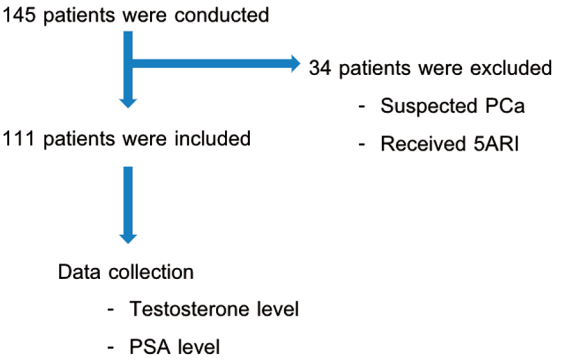

Figure 1. Consort diagram demonstrating the study flow.

of the present study was to evaluate normal PSA velocity (PSAV) or PSA change after TRT, which could be used as a crude reference during monitoring patients after TRT.

In terms of statistical analysis, patient characteristics data were described as a mean and a standard deviation or median and interquartile range (IQR) for continuous variables. A paired differences rate of testosterone and PSA level at time was analyzed by Wilcoxon signed-rank test to determine the difference between PSA changed after treatment. Statistical significance was defined as p-value of less than 0.05. All statistical analyses were performed with Stata, version 14 (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics

One hundred eleven patients were included for analysis. At the beginning of treatment, the mean age of the patients was 62 years. The mean body weight and body mass index was 73 kg and 26 kg/m^2, respectively. Among the patients, 17% had diabetes mellitus, 28% had essential hypertension, 33% had hypercholesterolemia, 1% had myocardial infarctions, 3% had metabolic syndromes, and 4% had cerebrovascular disease. Finally, the median serum testosterone was 247 ng/dL, and the median serum PSA was 1.16 ng/mL. Baseline patient characteristics are shown in Table 1.

Primary objectives

After collecting the data from testosterone deficiency patients with testosterone therapy, the testosterone level, and the PSA level at months 3, 6, 9, and 12, for a one year observation, were then reported as shown in Table 2. The median testosterone level was 247 ng/dL at baseline before starting TRT. The

Table 1. Baseline patient characteristics of the study population

Variable (unit)	n=111; n (%)
Age (year); mean±SD	62.72±10.64
Height (cm); mean±SD	166.20±5.76
Weight (kg); mean±SD	73.16±10.91
BMI (kg/m^2); mean±SD	26.47±3.69
Diabetes mellitus	17 (15.32)
Essential hypertension	28 (25.23)
Hypercholesterolemia	33 (29.73)
Myocardial infarction	1 (0.90)
Cerebrovascular disease	4 (3.60)
Metabolic syndrome	4 (3.60)
Type of TRT	
Transdermal testosterone gel	57 (51.35)
Oral testosterone undecanoate	40 (36.04)
Intramuscular testosterone undecanoate	14 (12.61)

BMI=body mass index; TRT=testosterone replacement therapy; SD=standard deviation

Table 2. Testosterone and PSA results before and after treatment

Laboratory results	Median (IQR)
Testosterone level (ng/dL) at	
Baseline (n=111)	247 (181, 294)
3 months (n=110)	314 (215, 443)
6 months (n=85)	270 (203, 357)
9 months (n=72)	333 (225, 474)
12 months (n=69)	307 (224, 420)
PSA level (ng/mL) at	
Baseline (n=108)	1.16 (0.61, 1.79)
3 months (n=93)	1.27 (0.81, 1.91)
6 months (n=75)	1.27 (0.83, 2.24)
9 months (n=69)	1.21 (0.77, 1.89)
12 months (n=62)	1.46 (0.92, 2.28)

PSA=prostate-specific antigen; IQR=interquartile range

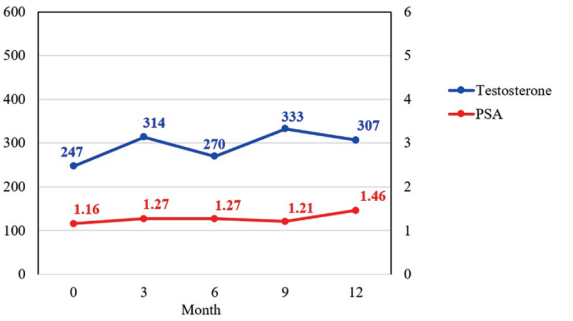

Figure 2. The serum testosterone and the PSA level before and after TRT during 1-year observation.

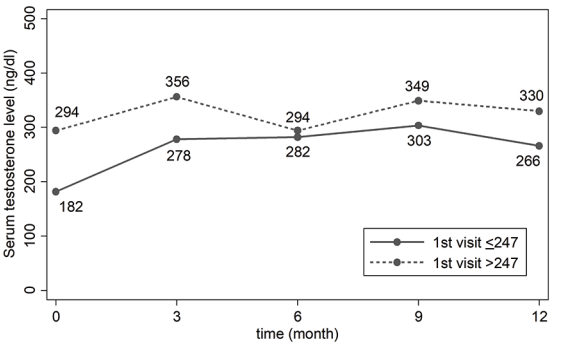

Figure 3. Serum testosterone level before and after treatment in the lower (≤ 247 ng/dL) and higher (>247 ng/dL) baseline testosterone level group.

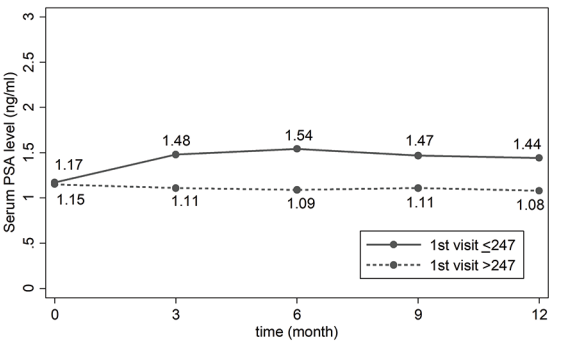

Figure 4. Serum PSA level before and after treatment in the lower (≤ 247 ng/dL) and higher (>247 ng/dL) baseline testosterone level group.

median testosterone level after treatment increased to 314 at 3 months, 270 at 6 months, 333 at 9 months, and 307 ng/dL at 12 months. In addition, the median PSA level was 1.16, 1.27, 1.27, 1.21, and 1.46 ng/mL at baseline, 3 months, 6 months, 9 months, and 12 months, respectively. All these results are shown in the Figure 2.

To further explore the testosterone level at the androgen receptor saturation point, the patients were divided into two groups according to their baseline serum testosterone levels, which were 247 ng/dL or less as the lower group and more than 247 ng/dL as the higher group. The median baseline testosterone levels were 182 and 294 ng/dL in the lower and higher testosterone group, respectively (Figure 3). Baseline PSA levels were 1.17 and 1.15 ng/mL in the lower and higher testosterone group respectively (Figure 4). Testosterone level significantly increased after treatment at three months in both groups as shown in Table 3. In the lower testosterone group, PSA level

Table 3. Summary of the testosterone and PSA changes compare between baseline and 3, 6, 9, and 12 months period in lower and higher baseline testosterone group

Laboratory results	n	Serum testosterone level (ng/dL); median (IQR)	p-value	n	Serum PSA level (ng/mL); median (IQR)	p-value
1st visit testosterone ≤247	56	182 (144, 210)		56	1.17 (0.57, 1.91)	
3 months	53	278 (188, 383)	<0.001	46	1.48 (0.71, 2.47)	0.003
6 months	44	282 (170, 364)	<0.001	37	1.54 (0.89, 2.30)	0.001
9 months	44	303 (207, 448)	<0.001	41	1.47 (0.77, 2.14)	0.010
12 months	38	266 (181, 412)	<0.001	32	1.44 (0.77, 2.31)	0.102
1st visit testosterone >247	55	294 (274, 328)		55	1.15 (0.67, 1.59)	
3 months	38	356 (283, 477)	0.001	33	1.11 (0.86, 1.61)	0.411
6 months	36	294 (242, 422)	0.632	31	1.09 (0.82, 1.54)	0.332
9 months	30	349 (249, 672)	0.047	26	1.11 (0.92, 1.78)	0.939
12 months	33	330 (258, 427)	0.046	28	1.08 (0.79, 1.71)	0.991

PSA=prostate-specific antigen; IQR=interquartile range

significantly increased during the first nine months after treatment (p=0.003, 0.001, and 0.01 at 3, 6, and 9 months, respectively) and was stable at 12 months, whereas PSA level in the higher testosterone group had non-significant changes during 12 the months period. These findings suggested that the prostate saturation point was at a testosterone level of 247 ng/dL.

Secondary objectives

The median PSA level was 1.16 ng/mL before TRT, which increased to 1.46 ng/mL after one year of treatment, translating to a mean PSAV of 0.3 ng/mL/year, as shown in the Figure 1. None of patient had PSA increased above 4 ng/mL after TRT, and no de novo prostate cancer occurred during the study period.

Discussion

Many recent publications have supported the prostate saturation theory, with a prostate saturation point of 250 ng/dL[13-16]. Testosterone above this level could not promote prostate growth and was not associated with prostate cancer risk[13-15].

The authors tested the prostate saturation model hypothesis by measuring changes in the PSA level after TRT in testosterone deficiency patients. In the patients who had low baseline testosterone levels, both testosterone and PSA levels increased more rapidly than the higher baseline testosterone level patients. PSA increased significantly during the first nine months. In contrast to the patients in higher baseline testosterone level group that PSA remained stable during the treatment period. The saturation point from the present study was a serum testosterone level of 247 ng/dL, almost equal to previous studies' findings[13-15]. The effect of testosterone on the prostate gland is an unresolved question. The recent literature demonstrated that TRT in testosterone deficiency patients did not increase risk of prostate cancer or even TRT in localized prostate cancer patient who had low testosterone level did not lead to prostate cancer progression[17,18]. The present study data supported the prostate saturation hypothesis that could be used to explain these findings.

The authors found that PSA increased by 0.3 ng/mL/year when compared to baseline. No patients had PSA level greater than 4 ng/mL during the follow-up period. Furthermore, there were no prostate cancer diagnoses during the follow-up period. The present study result was in the same direction with other clinical studies[19-21]. Cunningham et al found slightly increase in PSA by 0.47 ng/mL at 12 months after TRT compared to 0.06 ng/mL in the placebo group[19]. Permpongkosol el al[20] reported the long-term outcomes after TRT and demonstrated that PSA slightly increased during the first 24 months after treatment and remained steady until 96 months. Therefore, the authors believe that PSAV at 0.3 ng/mL/year was the physiologic PSAV after TRT and could be used as a rough reference range of PSA change during TRT in hypogonadal men. Additionally, TRT did not associate with prostate cancer risk over a short-term treatment period.

There are a limited number of clinical studies about testosterone deficiency in Thai populations, especially in old-age men or late-onset hypogonadism. The strength of the present study was that it was the first study that try to prove the concept of prostate saturation hypothesis in Thailand. Furthermore,

the authors excluded patients who had been treated with 5-alpha reductase inhibitors, which might affect PSA profile. Thus, the authors findings added more-scientific data to the field concerning the Thai population. The present study's results supported the prostate saturation hypothesis. Furthermore, it has clinical implications for the reference PSAV after TRT.

The present study had several limitations. There was limited data on the prostate volume because of the retrospective analyses. The authors did not routinely measure prostate size during follow-up. The authors believe that this was an important data point and would add more value to the study. The authors analyzed data within one year of follow-up because some patients had irregular follow-up during the treatment period after one year. This led to fluctuations in testosterone and PSA levels and probably made the results less accurate as they could have been. Therefore, the authors believe that a prospective study with longer follow-up would be of benefit to confirm the present study findings.

Conclusion

TRT significantly increased the serum testosterone level, but it had a limited effect on prostate changes. The present study results, based on Thai patients, support the prostate saturation model hypothesis. The authors believe that a testosterone level at 247 ng/dL can saturate all androgen receptors in the prostate gland and that higher levels do not increase prostate stimulation.

What is already known about this topic?

The effect of testosterone on the prostate gland is an unresolved question. The prostate saturation theory is the recent hypothesis that explained the effect of testosterone on prostate tissue. Serum testosterone level above at some point could not further stimulate prostate gland due to limited number of androgen receptors. However, the data in Thai population to support this hypothesis is limited.

What this study adds?

This study result supports the prostate saturation model hypothesis. The stimulation of testosterone has been limited by the number of androgen receptors and the testosterone level at 247 ng/dL is the saturation point. The present study is the first study of the prostate saturation hypothesis in Thailand and reports the implications for the reference PSAV during follow-up after TRT.

Acknowledgment

The authors acknowledge Ms. Suraida Aeesoa for statistical analysis, and support of this manuscript.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:2536-59.
2. Darby E, Anawalt BD. Male hypogonadism: an update on diagnosis and treatment. Treat Endocrinol 2005;4:293-309.
3. Miner M, Canty DJ, Shabsigh R. Testosterone replacement therapy in hypogonadal men: assessing benefits, risks, and best practices. Postgrad Med 2008;120:130-53.
4. Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. Int J Impot Res 2009;21:1-8.
5. Barqawi A, Crawford ED. Testosterone replacement therapy and the risk of prostate cancer. Is there a link? Int J Impot Res 2006;18:323-8.
6. Gore J, Rajfer J. Rising PSA during testosterone replacement therapy. Rev Urol 2004;6 Suppl 6:S41-3.
7. Gould DC, Kirby RS. Testosterone replacement therapy for late onset hypogonadism: what is the risk of inducing prostate cancer? Prostate Cancer Prostatic Dis 2006;9:14-8.
8. Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol 2008;159:507-14.
9. Eaton NE, Reeves GK, Appleby PN, Key TJ. Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies. Br J Cancer 1999;80:930-4.
10. Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 2008;100:170-83.
11. Morgentaler A. Guilt by association: a historical perspective on Huggins, testosterone therapy, and prostate cancer. J Sex Med 2008;5:1834-40.
12. Wu FC, Farley TM, Peregoudov A, Waites GM. Effects of testosterone enanthate in normal men: experience from a multicenter contraceptive efficacy study. World Health Organization Task Force on Methods for the Regulation of Male Fertility. Fertil Steril 1996;65:626-36.

13. Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. Eur Urol 2009;55:310-20.
14. Khera M, Bhattacharya RK, Blick G, Kushner H, Nguyen D, Miner MM. Changes in prostate specific antigen in hypogonadal men after 12 months of testosterone replacement therapy: support for the prostate saturation theory. J Urol 2011;186:1005-11.
15. 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;11:2818-25.
16. Khera M, Crawford D, Morales A, Salonia A, Morgentaler A. A new era of testosterone and prostate cancer: from physiology to clinical implications. Eur Urol 2014;65:115-23.
17. Twitchell DK, Pastuszak AW, Khera M. Controversies in testosterone therapy. Sex Med Rev 2021;9:149-59.
18. Santella C, Renoux C, Yin H, Yu OHY, Azoulay L. Testosterone Replacement therapy and the risk of prostate cancer in men with late-onset hypogonadism. Am J Epidemiol 2019;188:1666-73.
19. Cunningham GR, Ellenberg SS, Bhasin S, Matsumoto AM, Parsons JK, Preston P, et al. Prostate-specific antigen levels during testosterone treatment of hypogonadal older men: Data from a controlled trial. J Clin Endocrinol Metab 2019;104:6238-46.
20. Permpongkosol S, Khupulsup K, Leelaphiwat S, Pavavattananusorn S, Thongpradit S, Petchthong T. Effects of 8-year treatment of long-acting testosterone undecanoate on metabolic parameters, urinary symptoms, bone mineral density, and sexual function in men with late-onset hypogonadism. J Sex Med 2016;13:1199-211.
21. Sachdev S, Cucchiara AJ, Snyder PJ. Prostate-specific antigen concentrations in response to testosterone treatment of severely hypogonadal men. J Endocr Soc 2020;4:bvaa141.