JOMH
Journal of Men's Health

Editorial
DOI: 10.15586/jomh.v16iSP1.271

USE OF TESTOSTERONE REPLACEMENT THERAPY AFTER RADICAL PROSTATECTOMY MIGHT KILL TWO BIRDS WITH ONE STONE FROM THE PERSPECTIVE OF MEN'S HEALTH AND DISEASE CONTROL

Jong Kil Nam[1], Ki Soo Lee[2], Tae Nam Kim[3]

[1]Department of Urology, Pusan National University Yangsan Hospital, Yangsan, Korea

[2]Departments of Urology, College of Medicine, Dong-A University College of Medicine, Busan, South Korea

[3]Department of Urology, Biomedical Research Institute of Pusan National University Hospital, Pusan National University School of Medicine, Busan, Korea

Corresponding Author: Tae Nam Kim: bigman1995@hanmail.net

Submitted: 04 May 2020. Accepted: 05 June 2020. Published: 06 July 2020.

ABSTRACT

Testosterone plays an important role in promoting the differentiation and stimulation of prostate epithelial cells. Adding to the basic physiology of testosterone, several studies led to the dissemination of the historical androgen hypothesis that higher circulating androgen levels promote prostate cancer cell growth and make the tumor more aggressive. Whereas, the prostate saturation model accounted for the androgen sensitivity of testosterone stimulation in the prostate up to a saturation point, which occurred near the level of castration. Testosterone is related to prostate cancer metabolism in a complex manner; however, within the reference range, high or normal testosterone levels are expected to maintain benign and malignant prostate cells in a differentiated state. Accumulating evidence has suggested that testosterone replacement therapy (TRT) might prevent the development of prostate cancer and even reduce prostate cancer risk. There is no change in the clinical guidelines to be followed when considering TRT in patients with a history of prostate cancer, but it is necessary for the physician to inform patients of the positive effects of TRT on male health and prostate cancer.

Key Words: *Testosterone, Prostatic Cancer, Men's Health*

Testosterone plays an important role in promoting the differentiation and stimulation of prostate epithelial cells, where prostate cancer predominantly occurs.[1] In 1941, Huggins and Hodges discovered that the lowest serum testosterone level (upon castration) reduced the tumor burden in advanced prostate cancer; in 1996, Gann et al. reported that high levels of circulating testosterone within normal endogenous ranges were associated with increased risks of prostate cancer.[2,3] Adding to the basic physiology of testosterone, these studies led to the dissemination of the historical androgen hypothesis that high levels of circulating androgen promote prostate cancer cell growth and make the tumor more aggressive.

The prostate saturation model, which was proposed to replace the traditional testosterone-dependent model, accounted for the androgen sensitivity of testosterone stimulation in the prostate up to a saturation point, which occurred near the level of castration. According to this model, the intra-prostate tissue is sensitive to serum testosterone levels less than 120 ng/dL. In contrast, above this point, the androgen receptors in the prostate become saturated and insensitive to serum testosterone concentrations. Malignant prostate tissue was also expected to be unaffected by changes in serum testosterone concentrations beyond this saturation point.[4]

A study on the correlation between a faster age-related reduction in testosterone and an increased risk of developing prostate cancer demonstrated that an annual testosterone reduction of more than 30 ng/dL, compared to relatively stable testosterone levels, increased the incidence of prostate cancer by 5.03 times.[5] Mearini et al. reported that prostate cancer was frequently associated with low testosterone levels; moreover, a testosterone level less than 2.4 ng/mL was a strong independent predictor of prostate cancer (P=0.001).[6] The incidence of prostate cancer in the group with testosterone levels lower than 3.85 ng/mL was significantly higher than that in the group with higher testosterone levels (38.9% vs. 29.5%, P=0.018).[7] An important association between lower testosterone levels and more aggressive prostate cancer has been demonstrated. Lower basal testosterone levels are expected to be associated with a less differentiated cancer phenotype, poorer prognosis, and higher tumor burden before prostate cancer treatment. A significant decrease in the level of testosterone evoked the compensatory local endocrine system to maintain the testosterone concentrations in the prostate by the hyper-production of testosterone and the hyper-expression of androgen receptors. This change led to the hyper-stimulation of prostate cells, which resulted in DNA damage and increased the androgen receptor-driven proliferation of luminal cells. Consequently, neoplastic changes and cancer cell growth in the prostate were promoted.[8] Low testosterone levels are associated with increased micro-vessel formation in tumors, and an increase in androgen receptor density may induce the development of androgen-resistant or aggressive prostate cancer.[9] In a prospective study of 455 patients with clinically localized prostate cancer, a preoperative testosterone level less than 2.2 ng/mL was found to be associated with postoperative Gleason pattern grade 4–5 cancer (odds ratio [OR]: 2.4, P=0.48).[10] The preoperative total testosterone in locally advanced prostate cancer (pT3-4) was significantly lower than that in organ-confined disease.[11] A study including 338 patients eligible for active surveillance showed that preoperative low total testosterone levels (less than 300 ng/dL) were significantly associated with upgrading, upstaging, unfavorable disease, and positive surgical margins.[12]

Testosterone is related to prostate cancer metabolism in a complex manner. Calof et al.[13] analyzed 19 studies investigating the development of prostate cancer in men over the age of

45 receiving testosterone replacement therapy (TRT). The rate of prostate cancer in the TRT group was higher than that in the placebo group (OR: 1.09, 95% confidence interval [CI]: 0.48–2.49), which was not statistically significant.[14] Meanwhile, within the reference range, high or normal testosterone levels are expected to maintain benign and malignant prostate cells in a differentiated state. Although there was no well-designed study to assess the risk of developing prostate cancer in hypogonadal men taking exogenous testosterone, no significant difference in the prevalence of prostate cancer was observed in men receiving TRT compared to the placebo group.[14] Data in the last decade supported the hypothesis that TRT is not associated with an increased risk of developing prostate cancer and worse oncological outcomes in patients with prostate cancer. Accumulating evidence has suggested that TRT might prevent the development of prostate cancer and even reduce prostate cancer risk.[15] Several studies demonstrated the lower proportion of aggressive prostate cancer and the higher likelihood of favorable risk prostate cancer among patients who received prior TRT.[16,17]

Whether hypogonadal men with prostate cancer undergoing curative local therapy should be treated remains controversial. However, according to recent systematic reviews and meta-analyses, the risk of cancer progression appears to be minimal and the use of TRT in non-metastatic prostate cancer after definite local therapy is not associated with increased risk of biochemical recurrence (BCR), cancer recurrence, overall or disease-specific mortality, and salvage androgen deprivation therapy.[18,19] In contrast to the outcomes of the TRT effect to prevent the development of prostate cancer in patients with hypogonadism, there have been extremely limited studies showing that TRT may delay or prevent the recurrence of prostate cancer in patients with secondary hypogonadism who have received curative therapy. Pastuszak and Khera compared 103 hypogonadal and 49 eugonadal patients after radical prostatectomy to assess the safety of TRT.[20] BCR was only observed in high-risk patients, and the BCR rate in the high-risk TRT group (15%) remained significantly lower than that in the high-risk reference group (15% vs. 53%, P=0.02). They postulated that the lack of BCR in the TRT group was explained by the increased serum testosterone levels with unchanged residual intra-prostatic testosterone levels, thus implicating the saturation model. A very interesting study, reported in 2020, showed that TRT reduced the BCR and delayed the time to recurrence after radical prostatectomy.[21] One hundred and fifty-two patients on TRT, presenting delayed sexual function recovery with low preoperative and 3-month calculated free testosterone levels, were matched to 419 control patients not receiving TRT. During the median follow-up period of 3.4 years, the TRT group (7.2%) experienced less BCR than the control group (12.6%, P=0.07). In Cox regression analysis, TRT was revealed to be an independent predictor of recurrence-free survival with a 54% reduction in the risk of BCR (harzard ratio, 0.54, 95% CI: 0.292–0.997). Furthermore, the use of TRT delayed the time to recurrence by an average of 1.5 years in patients experiencing BCR. Ahlering et al. believed that their findings were logically explained. A lifestyle disease such as diabetes, obesity, or metabolic syndrome is intertwined with prostate cancer aggressiveness and low testosterone levels, which is considered a risk factor for BCR. They suggested that TRT after radical prostatectomy improved the metabolic status and restored the low testosterone levels to the normal range, which had a positive effect on male health and prostate cancer prognosis.

Since 2009, when the concept of the saturation model was introduced, many studies have been conducted on the association between testosterone concentrations and prostate cancer. Especially in recent decades, many research results have been

published contrary to the conventional relationship between testosterone and prostate cancer, and evidence is accumulating that testosterone below the castration level can increase the incidence of prostate cancer and worsen pathological outcomes. Owing to the absence of well-designed randomized controlled study results as well as long-term data showing that low testosterone levels can worsen male health and adversely affect the overall course of prostate cancer, many studies demonstrating that the use of TRT to manage these problems has a positive effect on prostate cancer prognosis continue to be published.[22,23] At this point, the attitude of the physician while treating patients with prostate cancer without recurrence, complaining of symptoms of secondary hypogonadism after definite local therapy, should also change.[24] There is no change in the clinical guidelines to be followed when considering TRT in patients with a history of prostate cancer, such as in-depth patient counseling and careful follow-up, but it is necessary for the physician to inform patients of the positive effects of TRT on male health and prostate cancer, only then should TRT be actively considered.

ACKNOWLEDGMENT

The authors would like to thank Editage (www.editage.co.kr) for English language editing.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

FUNDING

No financial support was received to conduct this research.

REFERENCES

1. Fujita K, Nonomura N. Role of androgen receptor in prostate cancer: A review. World J Mens Health 2019;37(3):288–95. https://doi.org/10.5534/wjmh.180040
2. Huggins C, Hodges CV. Studies on prostatic cancer. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin 1972;22(4):232–40. https://doi.org/10.3322/canjclin.22.4.232
3. Gann PH, Hennekens CH, Ma J, et al. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 1996;88(16):1118–26. https://doi.org/10.1093/jnci/88.16.1118
4. 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(2):310–20. https://doi.org/10.1016/j.eururo.2008.09.024
5. Wang K, Chen X, Bird VY, et al. Association between age-related reductions in testosterone and risk of prostate cancer—An analysis of patients' data with prostatic diseases. Int J Cancer 2017;141(9):1783–93. https://doi.org/10.1002/ijc.30882
6. Mearini L, Zucchi A, Nunzi E, et al. Low serum testosterone levels are predictive of prostate cancer. World J Urol 2013;31(2):247–52. https://doi.org/10.1007/s00345-011-0793-x
7. Shin BS, Hwang EC, Im CM, et al. Is a decreased serum testosterone level a risk factor for prostate cancer? A cohort study of Korean men. Korean J Urol 2010;51(12):819–23. https://doi.org/10.4111/kju.2010.51.12.819
8. Tafuri A, Sebben M, Shakir A, et al. Endogenous testosterone mirrors prostate cancer aggressiveness: Correlation between basal testosterone serum levels and prostate cancer European Urology Association clinical risk classes in a large cohort of Caucasian patients. Int Urol Nephrol 2020;52(7):1261-9. https://doi.org/10.1007/s11255-020-02398-x
9. Schatzl G, Madersbacher S, Haitel A, et al. Associations of serum testosterone with microvessel density, androgen receptor density and androgen receptor gene polymorphism in prostate cancer. J Urol 2003;169(4):1312–5. https://doi.org/10.1097/01.ju.0000056900.26628.16
10. Lane BR, Stephenson AJ, Magi-Galluzzi C, et al. Low testosterone and risk of biochemical recurrence and poorly differentiated prostate cancer at

radical prostatectomy. Urology 2008;72(6):1240–5. https://doi.org/10.1016/j.urology.2008.06.001
11. Massengill JC, Sun L, Moul JW, et al. Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. J Urol 2003;169(5): 1670–5. https://doi.org/10.1097/01.ju.0000062674.43964.d0
12. Ferro M, Lucarelli G, Bruzzese D, et al. Low serum total testosterone level as a predictor of upstaging and upgrading in low-risk prostate cancer patients meeting the inclusion criteria for active surveillance. Oncotarget 2017;8(11): 18424–34. https://doi.org/10.18632/oncotarget.12906
13. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: A meta-analysis of randomized, placebo-controlled trials. J Gerontol A 2005;60(11):1451–7. https://doi.org/10.1093/gerona/60.11.1451
14. Eaton NE, Reeves GK, Appleby PN, et al. Endogenous sex hormones and prostate cancer: A quantitative review of prospective studies. Br J Cancer 1999;80(7):930–4. https://doi.org/10.1038/sj.bjc.6690445
15. Wallis CJ, Lo K, Lee Y, et al. Survival and cardiovascular events in men treated with testosterone replacement therapy: An intention-to-treat observational cohort study. Lancet Diabetes Endocrinol 2016;4(6):498–506. https://doi.org/10.1016/S2213-8587(16)00112-1
16. Loeb S, Folkvaljon Y, Damber JE, et al. Testosterone replacement therapy and risk of favorable and aggressive prostate cancer. J Clin Oncol 2017;35:1430–6. https://doi.org/10.1200/JCO.2016.69.5304
17. Kaplan AL, Hu JC. Use of testosterone replacement therapy in the United States and its effect on subsequent prostate cancer outcomes. Urology 2013;82(82):321–6. https://doi.org/10.1016/j.urology.2013.03.049
18. Kardoust Parizi M, Abufaraj M, Fajkovic H, et al. Oncological safety of testosterone replacement therapy in prostate cancer survivors after definitive local therapy: A systematic literature review and meta-analysis. Urol Oncol 2019;37(10):637–46. https://doi.org/10.1016/j.urolonc.2019.06.007
19. Klap J, Schmid M, Loughlin KR. The relationship between total testosterone levels and prostate cancer: A review of the continuing controversy. J Urol 2015;193(2):403–13. https://doi.org/10.1016/j.juro.2014.07.123
20. Pastuszak AW, Pearlman AM, Lai WS, et al. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. J Urol 2013;190(2):639–44. https://doi.org/10.1016/j.juro.2013.02.002
21. Ahlering TE, Huynh LM, Towe M, et al. Testosterone replacement therapy reduces biochemical recurrence post-radical prostatectomy. BJU Int 2020;2. https://doi.org/10.1111/bju.15042
22. Hackett G. Type 2 diabetes and testosterone therapy. World J Mens Health 2019;37(1):31–44. https://doi.org/10.5534/wjmh.180027
23. Nam YS, Lee G, Yun JM, et al. Testosterone replacement, muscle strength, and physical function. World J Mens Health 2018;36(2):110–22. https://doi.org/10.5534/wjmh.182001
24. Bell MA, Campbell JD, Joice G, et al. Shifting the paradigm of testosterone replacement therapy in prostate cancer. World J Mens Health 2018;36(2):103–9. https://doi.org/10.5534/wjmh.170007