Original Research

Predictive factors for elevated prostate specific antigen and hematocrit levels during testosterone replacement therapy in patients with testosterone deficiency

Chung Heon Ryu[1,†], Sun Gu Park[1,†], Jeong Kyun Yeo[2], Min Gu Park[2,*]

[1]Department of Clinical Laboratory Science, Daejeon Health Institute of Technology, 34504 Daejeon, Republic of Korea
[2]Department of Urology, College of Medicine, Inje University, Seoul Paik Hospital, 04551 Seoul, Republic of Korea
*Correspondence: uromgpark@gmail.com; uromgpark@paik.ac.kr (Min Gu Park)
[†]These authors contributed equally.

Abstract

Objective: We examined risk factors associated with prostate specific antigen (PSA) and hematocrit (hct) elevation during testosterone replacement therapy (TRT) in patients with testosterone deficiency (TD). **Methods**: We retrospectively analyzed the medical records of patients receiving TRT for $\geq$3 months. We investigated the following parameters: age, body mass index, comorbidities, TRT type, TRT duration, pre-TRT prostate volume, pre- and post-TRT serological tests, prostate biopsies, prostate cancer diagnoses, pre- and post-TRT aging male symptom scale scores, hct elevation, and PSA elevation. The patients were divided into two groups based on the PSA elevation status for comparison, following which we analyzed the predictive factors for PSA elevation. They were also divided into two groups based on hct elevation status. **Results**: The PSA elevation group showed a statistically significantly higher mean age, pre-TRT prostate volume, and PSA level compared to the non-elevation group. The PSA non-elevation group showed a significantly higher percentage of smokers, while the PSA elevation group showed a statistically significantly higher prevalence of benign prostatic hyperplasia (BPH_LUTS). The results demonstrated that a large pre-TRT prostate volume, high pre-TRT PSA levels, BPH_LUTS, and being a non-smoker were the contributing factors for PSA elevation. The hct elevation group showed statistically significantly higher pre-TRT Hb, hct, and post-TRT testosterone levels, and dyslipidemia rates, as well as a non-statistically significant prevalence of testosterone enanthate (TE) and testosterone undecanoate (TU) intramuscular injection. The pre-TRT Hb and hct levels were contributing factors for hct elevation during TRT. TE injection showed marginal statistical significance. **Conclusions**: We identified large prostate volumes, high PSA levels, BPH_LUTS, and being non-smokers prior to TRT as risk factors for PSA elevation during TRT. Interestingly, we found that TRT-induced hct elevation was likely to occur in patients with high pre-TRT Hb and hct levels. Additionally, the hct levels should be monitored when using TE for TRT.

Keywords: testosterone; testosterone deficiency; testosterone replacement therapy; prostate specific antigen (PSA); hematocrit

1. Introduction

Testosterone replacement therapy (TRT) for men with testosterone deficiency (TD) is a relatively safe and effective treatment method that can be administered in various forms, including oral medication, transdermal gel, and injection [1]. TRT is generally contraindicated for patients with prostate cancer because of the risk of activation and growth of prostate cancer cells caused by TRT [2,3]. In fact, up to approximately a decade ago, there were concerns that TRT may exacerbate lower urinary tract symptoms because of prostatic hyperplasia and increased prostate cancer risk [4]. However, a study by Mogentaler *et al.* [5] reported no evidence of an association between prostate cancer and TRT. This result led to the introduction of the saturation theory. Specifically, the researchers hypothesized that although a temporary increase in the prostate volume and prostate specific antigen (PSA) levels may be found in the early stages of TRT, when the testosterone level in the prostate reaches a saturation point the TRT effect on the

prostate becomes weak [6]. As a result, the presence of associated lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH_LUTS) is no longer considered a contraindication for TRT. Hence, TRT is being administered with caution to patients with TD who have received radical treatment for prostate cancer and have no risk of recurrence for a sufficient period [7]. However, the elevation of the PSA levels (by $\geq$3 ng/dL) can sometimes occur after starting TRT despite normal pre-TRT PSA levels and digital rectal examination (DRE) results. In such cases, TRT is usually discontinued because of the concern for prostate cancer and PSA levels, and transrectal ultrasonography (TRUS), or DRE results are checked during follow-up observation. When necessary, a subsequent prostate biopsy is performed, which may confirm a diagnosis of prostate cancer in some patients. Most previous studies on the effects of TRT on PSA elevation and prostate cancer had a small sample size (<100 patients) or prostate biopsy was performed prior to TRT with a prospective study design. Accordingly, most of these studies investigated pa-

tients with TD without prostate cancer and, thus, do not reflect the distribution of patients encountered in clinical practice [8,9].

Another reason for discontinuing TRT (or for TRT dose reduction) is hematocrit (hct) elevation [10]. While there may be some differences when comparing guidelines, discontinuing TRT or attempts to lower the hct levels via phlebotomy are usually recommended when the hct levels are elevated by $\geq$52–54% [7,11]. Elevated hct levels pose the risk of facilitating cardiovascular blood clot formation by causing increased vascular blood viscosity and additional cardiovascular burden in patients with impaired cardiac function [12]. Thus, the hct levels must be checked regularly during TRT, with some cases resulting in the discontinuation of TRT with insufficient periods because of intolerable hct elevation. Typically, hct elevation is most commonly observed in older patients or those using short-acting injections, but empirical studies on this topic are lacking [10]. As the risk of cardiovascular thromboembolic events may be increased by hct elevation, identifying predictive factors may help lower the risk associated with TRT.

For these reasons, several guidelines have recommended periodic monitoring of the PSA and hct levels in patients undergoing TRT [11,13]. Accordingly, the present study aimed to analyze the risk factors associated with PSA and hct elevation to provide information for medical guidelines in terms of reducing the risk of adverse events commonly encountered during TRT in clinical practice.

2. Material and methods

Our study included patients diagnosed with TD between June 2010 and June 2019 at a urology outpatient clinic in a single hospital. Those who received $\geq$3 months of TRT were selected for enrollment. Their medical records were abstracted and reviewed for the following parameters: age, height, weight; presence and type of comorbidities (i.e., hypertension, diabetes mellitus, chronic kidney disease, hyperlipidemia, BPH_LUTS, cardiovascular disease, cerebrovascular disease, respiratory disease, and liver dysfunction), lifestyle, including smoking and drinking status, and the type of testosterone agent used during TRT (short-acting agents: oral testosterone undecanoate (TU) and 2% testosterone gel (T-gel); intermediate-acting agent: testosterone enanthate (TE) intramuscular (IM) injection; long-acting agent: testosterone undecanoate (TU) IM injection), duration of TRT (months); pre- and post-TRT serological test results (hemoglobin (Hb), hct, PSA, total testosterone, total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and glucose levels), pre-TRT prostate volume (measured in grams), hct elevation ($>$52%) during TRT; PSA elevation ($>$3.0 ng/mL) during TRT, prostate biopsies, prostate cancer diagnoses, Gleason scores (if diagnosed with prostate cancer), pre- and post-TRT aging male symptom scale (AMS) scores, and thromboembolic events.

Pre- and post-TRT differences among groups with and without PSA elevation were evaluated using independent t-tests and chi-squared tests. Logistic regression analyses were performed to identify the risk factors contributing to PSA elevation. The same statistical analysis procedures were applied for comparing pre- and post-TRT differences among groups with and without hct elevation and for evaluating risk factors contributing to hct elevation. The level of significance was set at $p < 0.05$. All statistical analyses were performed using statistical package for social sciences (SPSS) software (version 20.0; IBM Corp., Armonk, NY, USA).

3. Results

Among 964 patients receiving TRT at a single institution between June 2010 and June 2019, potential risk factors were abstracted and evaluated from the medical records of 566 patients who underwent $\geq$3-month TRT.

3.1 PSA elevation during TRT

Among a total of 566 patients, PSA elevation $\geq$3 ng/mL was observed in 60 patients (10.6%; Group 2). The mean duration of TRT until PSA elevation was 16.7 months. After discontinuing TRT because of PSA elevation, all patients received DRE and TRUS. After the use of antibiotics for suspected prostatitis or just follow-up of PSA, 41 patients resumed TRT after their PSA levels returned to normal and 19 patients (3.36%) underwent a prostate biopsy (i.e., trans-rectal ultrasound guided prostate biopsy; TRBx) owing to abnormal findings of DRE or TRUS that were suspicious for prostate cancer. If nodules were palpable in DRE or abnormal findings were observed in TRUS, TRBx was performed even if the PSA level was normalized after stopping TRT. TRBx was also recommended if the elevated PSA level did not fall below 3.0 ng/dL ($<$1.5 ng/mL in the case of taking 5-alpha reductase inhibitors) after discontinuation of TRT. If TRBx was recommended but the patient was unable to decide or aimed to postpone the examination, a prostate magnetic resonance imaging examination was performed to further confirm the need for TRBx. Of the patients undergoing TRBx, 6 (1.06%) were diagnosed with prostate cancer (localized prostate cancer). 5 patients were diagnosed with Gleason scores of 6 (3+3) and 1 patient presented with a Gleason score of 7 (3+4). There were no factors showing statistically significant differences among the 6 patients diagnosed with prostate cancer as compared with the 54 patients not diagnosed with prostate cancer despite PSA elevation.

3.2 Comparing the PSA elevation and non-elevation groups

The mean age of the enrolled patients was significantly higher in the PSA elevation (Group 2; 64.33 years) than in the non-elevation group (Group 1; 61.75 years, p = 0.024). The mean pre-TRT prostate volume was also

statistically significantly higher in Group 2 (35.36 g) than in Group 1 (28.90 g; $p < 0.001$). The pre-TRT PSA levels were statistically significantly higher in Group 2 (1.71 ng/mL) than in Group 1 (0.86 ng/mL; $p < 0.001$). There were no other statistically significant differences among the two groups concerning the other pre-TRT serological test results. The testosterone levels were higher in Group 2 (350.0 ng/mL) than in Group 1 (316.9 ng/mL), with a marginally significant difference ($p = 0.059$). The comparison of the pre-TRT AMS scores showed no statistically significant differences between the two groups (Table 1).

There was no difference in the percentage of drinkers when comparing the two groups (55.6% *vs.* 44.9%); the percentage of smokers was significantly higher in Group 1 (22.8%) than in Group 2 (9.8%; $p = 0.033$). Differences in the presence and types of comorbidities were investigated and the results showed no statistically significant differences in comorbidities with the exception of BPH_LUTS (28.3% *vs.* 43.3%, $p = 0.009$; Table 1). There were no statistically significant differences between the two groups after TRT.

3.3 Analysis of contributing factors for PSA elevation during TRT

The likelihood of PSA elevation during TRT was statistically significantly higher in patients with a high pre-TRT prostate volume or high pre-TRT PSA levels, in those receiving treatment for BPH-LUTS, and in non-smokers. There was no statistically significant association with TRT type and TRT duration (Table 2).

3.4 Comparing TRBx and non-TRBx groups

In total, 19 patients (Group 1) underwent TRBx based on the PSA follow-up period and DRE or TRUS results after discontinuation of TRT because of PSA elevation; 41 patients (Group 2) did not undergo TRBx because of the lack of specific findings upon TRUS or DRE as well as the normalization of PSA levels after discontinuing TRT. The comparison between the two groups showed no significant differences in age and weight, while the body mass index (BMI) was statistically significantly higher in Group 1 (26.8 kg/m^2) than in Group 2 (24.4 kg/m^2; $p = 0.049$). Group 1 also showed statistically significantly higher pre-TRT PSA levels (1.79 ng/mL *vs.* 0.95 ng/mL, $p = 0.001$). Our results showed no differences in the Hb, hct, total cholesterol, triglyceride, LDL, and blood glucose levels between the two groups, while Group 2 showed significantly higher mean HDL levels (37.9 mg/dL *vs.* 51.2 mg/dL; $p = 0.028$). There were no differences in the total testosterone levels, AMS scores, and smoking prevalence among the groups, while Group 1 showed a statistically significantly higher percentage of drinkers compared with Group 2 (61.1% *vs.* 32.3%, respectively; $p = 0.049$). No statistically significant differences in the type of testosterone agent used (until PSA elevation) were found between the two groups (Table 3).

Moreover, we found no differences in TRT duration (until PSA elevation; 21.95 months *vs.* 19.71 months, $p = 0.692$) and no significant differences in the elevated PSA levels (4.62 *vs.* 6.81, $p = 0.127$).

3.5 Risk factors for necessitating TRBx

Based on the factors showing differences between the TRBx and non-TRBx groups, a multivariate analysis was performed to identify influencing risk factors that necessitated TRBx. The factors showing statistical significance were identified to be pre-TRT PSA levels ($p = 0.023$) and drinking status ($p = 0.049$; Table 4).

3.6 Hct elevation during TRT

Among a total of 566 patients, hct elevation of $\geq 52\%$ was observed in 33 patients (5.83%). The mean duration of TRT until hct elevation was 16.7 months. There were no cases of cerebrovascular thromboembolic events occurring during TRT in this study. One patient in the hct non-elevation group received percutaneous coronary intervention (PCI) for coronary artery disease (CAD) during TRT, while two patients (one each from the hct elevation and non-elevation groups) received PCI for CAD at ≥ 1 year after the completion of TRT.

3.7 Comparing the hct elevation and non-elevation groups

After comparing the results of the two groups, Group 2 showed statistically significantly higher pre-TRT Hb and hct levels compared with Group 1 (Hb: 14.48 *vs.* 15.83, $p < 0.001$; hct: 42.25 *vs.* 46.5, $p < 0.001$). There were no differences between the two groups with respect to age, weight, BMI, smoking status, drinking status, and serological test results (i.e., lipid profile, blood glucose levels, and total testosterone levels). Moreover, there was no difference in the pre-TRT AMS scores between the two groups. Regarding the type of TRT used, the percentage of patients who received TE IM injection was higher in Group 2 than in Group 1 (41.8% *vs.* 45.5%, respectively) and the prevalence of TU IM injection was higher in Group 2 than in Group 1 (27.1% *vs.* 39.4%, respectively), although the differences were not statistically significant. The mean post-TRT testosterone levels were significantly higher in Group 2 than in Group 1 (714.78 ng/mL *vs.* 933.04 ng/mL, respectively; $p = 0.009$) and the margin of increase in the testosterone levels was statistically significantly higher ($p = 0.014$). Regarding the AMS scores, the psychological sub-domain scores were statistically significantly lower in Group 2 than in Group 1 ($p = 0.033$). The percentage of patients with dyslipidemia was statistically significantly higher in Group 2 than in Group 1 (20.5% *vs.* 44.8%, respectively; $p = 0.002$; Table 5).

3.8 Factors contributing to hct elevation during TRT

Multivariate analysis results identified pre-TRT Hb ($p = 0.013$) and hct ($p < 0.001$) levels as statistically signifi-

Table 1. Comparative medical and demographic characteristics of the patients in the PSA elevation group (>3 ng/mL) during testosterone treatment (Group 2) compared with those of patients in the non-elevation group (Group 1).

	Group 1 (n = 506)	Group 2 (n = 60)	p-value*
	Mean ± SD	Mean ± SD	
Age (years)	61.75 ± 8.38	64.33 ± 8.31	0.024
BMI (kg/m^2)	25.21 ± 4.15	25.81 ± 4.26	0.347
Prostate volume (g)	28.90 ± 8.88	35.36 ± 11.80	<0.001
PSA (ng/mL)	0.86 ± 0.58	1.71 ± 0.88	<0.001
Hemoglobin (g/dL)	14.58 ± 1.42	14.33 ± 1.25	0.202
Hematocrit (%)	42.54 ± 4.24	41.90 ± 3.45	0.273
Total cholesterol (mg/dL)	182.07 ± 42.20	181.38 ± 35.83	0.909
Triglyceride (mg/dL)	165.71 ± 110.80	166.97 ± 133.73	0.950
LDL cholesterol (mg/dL)	109.41 ± 34.08	105.41 ± 33.62	0.523
HDL cholesterol (mg/dL)	50.09 ± 11.37	48.61 ± 14.60	0.481
Glucose (mg/dL)	123.45 ± 51.58	118.55 ± 35.78	0.502
Testosterone (ng/mL)	316.89 ± 124.01	350.00 ± 143.50	0.059
AMS scale			
Somato-vegetative	12.45 ± 6.42	13.10 ± 5.87	0.654
Psychological	7.13 ± 3.88	7.86 ± 3.62	0.405
Sexual	10.60 ± 5.41	12.95 ± 4.27	0.052
Total score	30.48 ± 14.40	30.05 ± 15.70	0.895
Treatment type			0.073
Short-acting type	152/506 (30.0)	26/59 (44.1)	
Intermediate-acting type	215/506 (42.5)	18/59 (30.5)	
Long-acting type	139/506 (27.5)	15/59 (25.4)	
Drinking, n (%)			0.158
No	154/347 (44.4)	27/49 (55.1)	
Yes	193/347 (55.6)	22/49 (44.9)	
Smoking, n (%)			0.033
No	277/359 (77.2)	46/51 (90.2)	
Yes	82/359 (22.8)	5/51 (9.8)	
Comorbidities			
None	174/506 (34.4)	14/60 (23.3)	0.086
BPH_LUTS	143/506 (28.3)	26/60 (43.3)	0.009
Hypertension	184/506 (36.4)	23/60 (38.3)	0.697
Diabetes mellitus	122/506 (24.1)	16/60 (26.7)	0.615
Dyslipidemia	97/506 (19.2)	8/60 (13.3)	0.275
Hepatobiliary disease	36/506 (7.1)	1/60 (1.7)	0.109
Pulmonary disease	21/506 (4.2)	7/60 (11.7)	0.060

AMS, Aging Male Symptom Scale; BMI, body mass index; BPH_LUTS, benign prostatic hyperplasia with lower urinary tract symptoms; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSA, prostate specific antigen; SD, standard deviation; short-acting type, oral testosterone undecanoate, testosterone gel; intermediate-acting type, testosterone enanthate intramuscular injection; long-acting type, testosterone undecanoate intramuscular injection.
*Results of independent t-tests or chi-squared tests.

cant contributing factors for hct elevation, while the use of TE IM injection showed marginal significance ($p = 0.069$; Table 6).

3.9 Other adverse effects during TRT

21 patients (3.71%) experienced other adverse events such as injection site pain, hot flushing, acne, and edema

Table 2. Multivariate analysis results based on logistic regression performed for clinical factors associated with PSA elevation occurring during testosterone treatment.

	β	SE	p-value	Exp (β)	CI
Age (years)	0.042	0.028	0.126	1.043	0.988–1.102
Prostate volume (g)	0.039	0.017	0.020	1.040	1.006–1.074
PSA (ng/mL)	1.134	0.235	<0.001	3.108	1.961–4.926
BPH_LUTS	1.086	0.401	0.007	2.961	1.348–6.503
Lung disease	0.775	0.591	0.190	2.170	0.681–6.913
Smoking	−1.449	0.674	0.032	0.235	0.063–0.880
TD <6 months			0.336		
TD 6–12 months	−0.897	0.762	0.239	0.408	0.092–1.815
TD 12–24 months	−1.566	0.871	0.072	0.209	0.038–1.150
TD >24 months	−0.700	0.689	0.310	0.497	0.129–1.916
Short-acting type			0.161		
Intermediate-acting type	−0.800	0.505	0.114	0.449	0.167–1.210
Long-acting type	0.111	0.536	0.835	1.118	0.391–3.194

BPH_LUTS, benign prostatic hyperplasia and associated lower urinary tract symptoms; CI, confidence interval; PSA, prostate specific antigen; TD, testosterone treatment duration; short-acting type, oral testosterone undecanoate, testosterone gel; intermediate-acting type, testosterone enanthate intramuscular injection; long-acting type, testosterone undecanoate intramuscular injection.

in the order of frequency, and all adverse events recovered without any special sequelae.

4. Discussion

TRT has many beneficial effects for hypogonadal men. However, it can also cause various adverse effects, including gynecomastia, elevated estrogen levels, skin problems (i.e., acne and edema), and erythrocytosis [13]. TRT-induced erythrocytosis is typically defined according to Hb levels >18.5 g/dL and hct levels >52% [14]. Physiologically, erythrocytosis is defined as an erythrocyte mass exceeding 125% of predicted levels based on sex and body mass [15]. Generally, an increase in red blood cell mass causes increased blood viscosity, leading to reduced venous return and increased platelet adhesiveness; hence, this adverse effect could increase the risk of thromboembolism and myocardial infarction [16]. The mechanism by which TRT causes erythrocytosis can be explained via the respective roles of hepcidin, iron sequestration and turnover, erythropoietin formation, bone marrow stimulation, and genetic factors [10]. Erythrocytosis is likely determined by the duration of supraphysiological testosterone levels because of the combination of exogenous testosterone type, dose, and pharmacokinetics [17]. It is known that the incidence of erythrocytosis after testosterone cypionate or enanthate IM injection is high (approximately 40%) [17]. Erythrocytosis may occur readily since these testosterone agents could reach a supraphysiological level within a short time [17]. In the present study, the comparison of the obtained results between the hct elevation and non-elevation groups showed no statistically significant differences concerning the types of testosterone agents administered. How-

ever, the percentage of patients receiving TE and TU IM injections was higher in the hct elevation than in the non-elevation group. Unlike a prospective study that typically recruits participants after setting the dose and duration of TRT, the patients in this study had a low incidence of erythrocytosis owing to varying intervals with respect to TE injections (2–4 weeks), and the mean duration until hct elevation was longer (16.7 months) compared to that reported in a previous prospective study (10.5 ± 9.1 months) [18]. It is known that T-gel and TU IM injections usually result in maintenance of the testosterone levels within physiological levels [19,20]. However, these testosterone agents have the potential to elevate testosterone to a supraphysiological level depending on the dose or injection interval; thus, the risk of erythrocytosis may appear unexpectedly in early-stage treatment if the dose and injection interval are not adjusted for each patient. In the present study, the hct elevation group showed a significantly higher increase in the testosterone levels compared with the non-elevation group. With respect to contributing factors for hct elevation, the pre-TRT Hb and hct levels demonstrated statistical significance. Thus, close attention should be paid to monitoring the risk of erythrocytosis during TRT among patients with high pre-TRT Hb and hct levels. Dose and injection intervals should be adjusted for these patients. Although statistical significance was not confirmed in this study, TE injection showed marginal statistical significance as a contributing factor for hct elevation. Thus, we conclude that oral TU or T-gel should be chosen instead of TE or TU IM injections for patients with high pre-TRT Hb and hct levels. In addition, an increase in the hct levels may also depend on the nutritional status, food consumption, or other

Table 3. Comparison of baseline medical and demographic characteristics between the prostate biopsy (Group 1) and the non-prostate biopsy group (Group 2).

	Group 1 (n = 19)	Group 2 (n = 41)	p-value*
	Mean ± SD	Mean ± SD	
Age (years)	63.74 ± 7.97	64.66 ± 8.52	0.692
Weight (kg)	75.04 ± 9.92	70.52 ± 11.49	0.167
BMI (kg/m^2)	26.84 ± 4.66	24.38 ± 3.74	0.049
Prostate volume (g)	24.79 ± 13.16	35.15 ± 11.30	0.913
PSA (ng/mL)	1.79 ± 0.92	0.95 ± 0.86	0.001
Hemoglobin (g/dL)	13.78 ± 0.88	13.90 ± 1.34	0.724
Hematocrit (%)	40.89 ± 2.65	41.65 ± 3.68	0.433
Total cholesterol (mg/dL)	180.81 ± 38.19	180.92 ± 36.28	0.992
Triglyceride (mg/dL)	255.14 ± 224.29	140.62 ± 96.78	0.231
LDL cholesterol (mg/dL)	104.14 ± 31.87	104.59 ± 35.21	0.976
HDL cholesterol (mg/dL)	37.86 ± 12.77	51.17 ± 14.01	0.028
Glucose (mg/dL)	133.31 ± 36.33	114.46 ± 37.63	0.097
Testosterone (ng/mL)	375.22 ± 167.44	335.75 ± 133.19	0.340
AMS scale			
Somato-vegetative subscale	13.29 ± 4.46	12.20 ± 7.09	0.716
Psychological subscale	7.71 ± 3.55	7.73 ± 3.73	0.991
Sexual subscale	12.29 ± 4.92	13.00 ± 4.07	0.723
Total score	29.43 ± 16.39	29.93 ± 15.47	0.945
Latest treatment type			0.408
Short-acting type	10/19 (52.6)	15/41 (36.6)	
Intermediate-acting type	4/19 (21.1)	15/41 (36.6)	
Long-acting type	5/19 (26.3)	11/41 (26.8)	
Drinking, n (%)			0.049
No	7/18 (38.9)	21/31 (67.7)	
Yes	11/18 (61.1)	10/31 (32.3)	
Smoking, n (%)			0.443
No	16/18 (88.9)	31/33 (93.9)	
Yes	2/18 (11.1)	2/33 (6.1)	

AMS, Aging Male Symptom Scale; BMI, body mass index; SD, standard deviation; short-acting type, oral testosterone undecanoate, testosterone gel; intermediate-acting type, testosterone enanthate intramuscular injection; long-acting type, testosterone undecanoate intramuscular injection; PSA, prostate specific antigen.

*Results of independent t-tests or chi-squared tests.

Table 4. Multivariate analysis results based on logistic regression performed to examine the parameters contributing to prostate biopsy risk.

	β	SE	p-value	Exp (β)	CI
BMI (kg/m^2)	–0.429	0.735	0.560	0.651	0.154–2.752
PSA (ng/mL)	2.858	1.261	0.023	17.433	1.471–206.598
HDL cholesterol (mg/dL)	–0.131	0.120	0.273	0.877	0.694–1.109
Glucose (mg/dL)	0.013	0.027	0.637	1.013	0.961–1.067
Drinking	4.022	2.044	0.049	55.788	1.016–3063.710

BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; PSA, prostate specific antigen; SE, standard error.

physiological status [21,22]. However, this study could not confirm sufficient information on this issue because of its retrospective study design.

PSA is known to be associated with the progression of BPH_LUTS, while also showing a strong correlation with prostate volume [23]. Accordingly, our findings indicated that the PSA elevation group during TRT presented signifi-

Table 5. Comparison of baseline medical and demographic characteristics between the hematocrit (hct) elevation (>52%; Group 2) and the non-hct elevation group (Group 1) during testosterone treatment.

	Group 1 (n = 495)	Group 2 (n = 33)	p-value*
	Mean ± SD	Mean ± SD	
Age (years)	61.93 ± 8.33	60.21 ± 8.02	0.250
Weight (kg)	71.62 ± 10.04	73.38 ± 7.95	0.432
BMI (kg/m^2)	25.18 ± 3.50	25.43 ± 2.25	0.742
Prostate volume (g)	29.71 ± 9.71	29.67 ± 8.97	0.983
PSA (ng/mL)	0.96 ± 0.68	0.94 ± 0.59	0.916
Hemoglobin (g/dL)	14.48 ± 1.40	15.83 ± 1.11	<0.001
Hematocrit (%)	42.25 ± 4.16	46.50 ± 2.95	<0.001
Total cholesterol (mg/dL)	182.12 ± 42.48	185.48 ± 39.59	0.700
Triglyceride (mg/dL)	165.62 ± 114.18	164.13 ± 118.90	0.961
LDL cholesterol (mg/dL)	109.52 ± 34.01	103.33 ± 43.71	0.503
HDL cholesterol (mg/dL)	49.72 ± 11.47	50.67 ± 11.68	0.755
Glucose (mg/dL)	122.77 ± 51.00	116.96 ± 36.25	0.582
Testosterone (ng/mL)	319.37 ± 121.68	322.20 ± 180.24	0.902
AMS scale			
Somato-vegetative	12.71 ± 6.31	11.29 ± 6.97	0.373
Psychological	7.21 ± 3.96	6.83 ± 3.00	0.694
Sexual	10.54 ± 5.43	11.88 ± 4.77	0.319
Total score	30.42 ± 14.68	32.71 ± 10.34	0.528
Latest treatment type			0.111
Short-acting type	154/495 (31.1)	5/33 (15.2)	
Intermediate-acting type	207/495 (41.8)	15/33 (45.5)	
Long-acting type	134/495 (27.1)	13/33 (39.4)	
Drinking, n (%)			0.382
No	163/349 (46.7)	9/24 (37.5)	
Yes	186/349 (53.3)	15/24 (62.5)	
Smoking, n (%)			0.929
No	285/365 (78.1)	17/22 (77.3)	
Yes	80/365 (21.9)	5/22 (22.7)	
Comorbidities (%)			
None	169/409 (41.3)	8/29 (27.6)	0.243
BPH_LUTS	149/409 (36.4)	8/29 (27.6)	0.337
Hypertension	179/409 (43.8)	12/29 (41.4)	0.802
Diabetes Mellitus	119/409 (29.1)	8/29 (27.6)	0.863
Dyslipidemia	84/409 (20.5)	13/29 (44.8)	0.002
Hepatobiliary disease	33/409 (8.1)	3/29 (10.3)	0.433
Pulmonary disease	24/409 (5.9)	2/29 (6.9)	0.527

AMS, Aging Male Symptom Scale; BMI, body mass index; BPH_LUTS, benign prostatic hyperplasia associated with lower urinary tract symptoms; short-acting type, oral testosterone undecanoate, testosterone gel; intermediate-acting type, testosterone enanthate intramuscular injection; long-acting type, testosterone undecanoate intramuscular injection; SD, standard deviation.

*Results of independent t-tests or chi-squared tests.

cantly higher pre-TRT PSA levels, higher pre-TRT prostate volumes, and a higher pre-TRT incidence of patients receiving treatment for BPH_LUTS compared with the non-PSA elevation group. These findings could be attributed to the fact that these three factors are strongly associated with each other. The PSA elevation group showed a mean PSA level of 1.71 ng/mL and a prostate volume of 35.4 g, which were not substantially different compared to PSA levels ≥1.5 and prostate volumes ≥30 g that are used as the criteria for predicting BPH_LUTS progression [23–25]. According to current TRT guidelines, BPH_LUTS is not a contraindication for TRT [7,11]. However, the findings of our study demonstrated that the PSA levels, prostate volume, and BPH_LUTS treatment were statistically significant influencing factors for PSA elevation occurring during TRT. Therefore, caution should be taken with respect to possible

Table 6. Multivariate analysis results based logistic regression performed for evaluating clinical factors associated with hct elevation.

	β	SE	p-value	Exp (β)	CI
Hemoglobin (g/dL)	−1.421	0.573	0.013	0.241	0.079–0.742
Hematocrit (%)	3.332	0.942	<0.001	27.988	4.415–177.450
Hyperlipidemia	1.155	1.239	0.351	3.174	0.280–36.010
△Testosterone (ng/mL)	0.001	0.001	0.562	1.001	0.999–1.003
Short-acting type			0.188		
Intermediate-acting type	4.134	2.272	0.069	62.417	0.726–5363.865
Long-acting type	2.938	1.959	0.134	18.885	0.406–878.993

△, Difference before and after testosterone treatment; CI, confidence interval; hct, hematocrit; short-acting type, oral testosterone undecanoate, testosterone gel; intermediate-acting type, testosterone enanthate intramuscular injection; long-acting type, testosterone undecanoate intramuscular injection.

PSA elevation during TRT when patients being treated for BPH_LUTS present with prostate volumes ≥35 g and PSA levels ≥1.71 g/dL.

Among the 566 patients receiving TRT for ≥3 months, 19 patients (3.36%) received TRBx. Concerning the contributing factors for TRBx (due to PSA elevation occurring during TRT), the pre-TRT PSA levels and drinking status were identified to be statistically significant risk factors. In the past, there was a preconception that TRT increases the risk for prostate cancer. However, this led to misunderstanding as the prostate is an androgen sensitive organ. A study by Shoskes et al. [26] analyzed prostate biopsy results from before and after TRT in male patients with hypogonadism, demonstrating that TRT does not promote prostate cancer [26]. Similarly, the American Urological Association guidelines specify that TRT does not increase the risk of prostate cancer development [7]. However, elevated PSA levels during TRT within clinical practice would raise concerns regarding prostate cancer caused by TRT. As presented in this study, most patients with PSA elevation (68%) showed no specific findings in DRE or TRUS and, therefore, they resumed TRT after normalization of the PSA levels (following treatment for inflammation and subsequent re-examination). Nonetheless, when TRBx becomes necessary, both the physician and patient inevitably feel burdened. In this study, 19/60 patients (31.7%) with PSA elevation ultimately underwent TRBx. If a patient group could be predicted in advance, closer attention could be paid during TRT and the patients could be provided with more comprehensive information regarding the benefits and risks of TRT prior to TRT treatment.

Among the 60 patients with PSA elevation occurring during TRT within the current study, the TRBx group showed a statistically significantly higher percentage of drinkers (61.1%) compared with the non-TRBx group. High BMI and low HDL levels are believed to reflect the characteristics of the TRBx group to a certain degree; specifically, this group includes a high percentage of drinkers. A study by Zhao et al. [27] reported that the risk of prostate cancer was 1.22 times higher among drinkers compared with non-drinkers ($p < 0.05$), while another study reported a dose-response relationship between alcohol intake and prostate cancer risk [27]. Since drinking itself could be considered a risk factor of prostate cancer, if pre-TRT assessment results show high prostate volumes and PSA levels that could potentially lead to prostate disease and the patient enjoys drinking, then, the possibility of PSA elevation during TRT leading to TRBx should be considered and sufficient explanation concerning the risks associated with TRT should be provided to the patient prior to TRT.

In analyzing the contributing factors for PSA elevation occurring during TRT, we found that PSA elevation occurred more frequently among non-smokers. In this regard, Li et al. [28] reported that smokers showed statistically significantly lower PSA levels compared with non-smokers among men aged ≥40 years [28]. Similarly, Kristal et al. [29] reported that smokers showed statistically significantly lower PSA levels compared with non-smokers among men aged ≥55 years [29]. Similar results were found in a study by Gelmann et al. [30], who compared the PSA levels among smokers and non-smokers aged ≥55 years. Although the etiology mediating negative correlations between smoking and PSA levels cannot be clearly understood, it is suspected that smokers have increased levels of circulating sex hormone-binding globulins that may inhibit PSA production [31]. In contrast, a study by Koc et al. [32] reported statistically significantly high PSA levels in smokers [32]. Moreira et al. [33] reported similar results, indicating that smoking is correlated with acute and chronic prostatic inflammation based on the reduction by dutasteride of prostate cancer events (REDUCE) study results. Therefore, additional studies are needed on the relationship among the smoking and PSA levels. To the best of our knowledge, this is the first study reporting an association between PSA elevation during TRT and smoking status. Thus, if any patient being treated for BPH_LUTS has a large prostate volume and slightly elevated PSA levels prior to TRT, more attention should be paid to that patient's smoking status.

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This study had some limitations. The most significant limitation was the fact that the study retrospectively analyzed patient medical records. Thus, comorbidities, drinking, and smoking status may not have been recorded accurately. Moreover, as the applied dose for TRT was not the same (unlike in prospective studies), differences based on administered testosterone agents may not appear clearly. With respect to treatment intervals, there may be difficulties in comparing therapeutic effects due to differences in injection intervals among patients. Moreover, in contrast to a prospective study format, the time points for serological tests and symptom questionnaires in this study were not consistent. This could cause difficulties in interpreting our study results. In addition, the number of patients diagnosed with prostate cancer or thromboembolic events was very small. Therefore, a meaningful analysis of their characteristics could not be performed. Nonetheless, the present study directly analyzed data from clinical practice (*vs.* a research environment) to identify predictive factors for PSA and hct elevation during TRT. In that respect, our findings are expected to provide valuable information to clinicians who actually perform TRT.

5. Conclusions

Based on the obtained findings, we conclude that there is a high likelihood of PSA elevation occurring during TRT in patients with high pre-TRT PSA levels, large pre-TRT prostate volumes, or among those receiving treatment for BPH_LUTS. PSA elevation during TRT appeared more frequently among non-smokers, while drinkers with PSA elevation were more likely to require prostate biopsy. Moreover, patients with high pre-TRT Hb and hct levels were more likely to show hct elevation during TRT. Additionally, the hct levels should also be monitored when using TE for TRT.

Abbreviations

AMS, Aging Male Symptom Scale; BPH_LUTS, benign prostatic hyperplasia; CAD, coronary artery disease; DRE, digital rectal examination; IM, intramuscular; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; PSA, prostate specific antigen; TD, testosterone deficiency; TE, testosterone enanthate; T-gel, testosterone gel; TRBx, trans-rectal ultrasound guided prostate biopsy; TRT, testosterone replacement therapy; TRUS, transrectal ultrasonography; TU, testosterone undecanoate.

Author contributions

Study conception and design—MGP, CHR, SGP and JKY. Data acquisition—JKY and MGP. Analysis and interpretation of data—CHR and SGP. Drafting the article—MGP.

Ethics approval and consent to participate

All investigations in studies involving medical data of patients were in accordance with the ethical standards of the institutional research review board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The present study protocol was reviewed and approved by the Institutional Review Board of Seoul Paik Hospital (IRB No.: 2020-04-009) and informed consent was not required because of the retrospective nature of this study.

Conflicts of interest

The authors declare no conflict of interest. MGP is serving as one of the Guest editors of this journal. We declare that MGP had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to AT.

References

[1] Hackett G, Cole N, Mulay A, Strange RC, Ramachandran S. Long-Term Testosterone Therapy in Type 2 Diabetes Is Associated with Decreasing waist circumference and improving erectile function. The World Journal of Men's Health. 2020; 38: 68–77.

[2] Bhasin S, Brito JP, Cunningham GR *et al*. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism. 2018; 103: 1715–1744.

[3] Kim M, Byun SS, Hong SK. Testosterone Replacement Therapy in Men with Untreated or Treated Prostate Cancer. The World Journal of Mmen's Health 2021; 39: 705–723.

[4] 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. European Journal of Endocrinology. 2008; 159: 507–514.

[5] Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. European Urology. 2006; 50: 935–939.

[6] Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and. The limits of androgen-dependent growth. European Urology. 2009; 55: 310–320.

[7] Mulhall JP, Trost LW, Brannigan RE, Kurtz EG, Redmon JB, Chiles KA, *et al*. Evaluation and Management of Testosterone Deficiency: AUA Guideline. The Journal of Urology. 2018; 200: 423–432.

[8] Rhoden EL, Morgentaler A. Influence of demographic factors and biochemical characteristics on the. prostate-specific anti-

gen (PSA) response to testosterone replacement therapy. International Journal of Impotence Research. 2006; 18: 201–205.

[9] Coward RM, Simhan J, Carson CC, 3rd. Prostate-specific antigen changes and prostate cancer in hypogonadal men treated with testosterone replacement therapy. BJU International. 2009; 103: 1179–1183.

[10] Ohlander SJ, Varghese B, Pastuszak AW. Erythrocytosis Following Testosterone Therapy. Sexual Medicine Reviews. 2018; 6: 77–85.

[11] Mirone V, Debruyne F, Dohle G, et al. European Association of Urology Position Statement on the Role of the Urologist in the management of male hypogonadism and testosterone therapy. European Urology. 2017; 72: 164–167.

[12] Hayden RP, Bennett NE, Tanrikut C. Hematocrit Response and Risk Factors for Significant Hematocrit Elevation with implantable testosterone pellets. The Journal of Urology. 2016; 196: 1715–1720.

[13] Lee DS, Park HJ. Efficacy and Safety of Testosterone Therapy Based on Guideline Recommendations; re: Clinical Practice Guideline by the American College of Physicians. The World Journal of Men's Health. 2020; 38: 397.

[14] Shahidi NT. Androgens and erythropoiesis. The New England Journal of Medicine. 1973; 289: 72–80.

[15] Keohane C, McMullin MF, Harrison C. The diagnosis and management of erythrocytosis. BMJ. 2013; 347: f6667.

[16] Braekkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Hansen JB. Hematocrit and risk of venous thromboembolism in a general population. The Tromso study. Haematologica. 2010; 95: 270–275.

[17] Ip FF, di Pierro I, Brown R, Cunningham I, Handelsman DJ, Liu PY. Trough serum testosterone predicts the development of polycythemia in hypogonadal men treated for up to 21 years with subcutaneous testosterone pellets. European Journal of Endocrinology. 2010; 162: 385–390.

[18] Pastuszak AW, Gomez LP, Scovell JM, Khera M, Lamb DJ, Lipshultz LI. Comparison of the Effects of Testosterone Gels, Injections, and Pellets on Serum hormones, erythrocytosis, lipids, and prostate-specific antigen. Sexual Medicine Reviews. 2015; 3: 165–173.

[19] Schubert M, Minnemann T, Hübler D, et al. Intramuscular testosterone undecanoate: pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. The Journal of Clinical Endocrinology and Metabolism. 2004; 89: 5429–5434.

[20] Swerdloff RS. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. Journal of Clinical Endocrinology & Metabolism. 2000; 85: 4500–4510.

[21] Patnaik MM, Tefferi A. The complete evaluation of erythrocytosis: congenital and acquired. Leukemia. 2009; 23: 834–844.

[22] Montero D, Lundby C. Red cell volume response to exercise training: Association with aging. Scandinavian Journal of Medicine & Science in Sports. 2017; 27: 674–683.

[23] Bohnen AM, Groeneveld FP, Bosch JL. Serum prostate-specific antigen as a predictor of prostate volume in the community. European Urology. 2007; 51: 1645–1652.

[24] Roehrborn CG, Boyle P, Gould AL, Waldstreicher J. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. Urology. 1999; 53: 581–589.

[25] Mochtar CA, Kiemeney LA, van Riemsdijk MM et al. Prostate-specific antigen as an estimator of prostate volume in the management of patients with symptomatic benign prostatic hyperplasia. European Urology. 2003; 44: 695–700.

[26] Shoskes DA, Barazani Y, Fareed K, Sabanegh E, Jr. Outcomes of Prostate Biopsy in Men with Hypogonadism Prior or During Testosterone replacement therapy. International Brazilian Journal of Urology. 2015; 41: 1167–1171.

[27] Zhao J, Stockwell T, Roemer A, Chikritzhs T. Is alcohol consumption a risk factor for prostate cancer? A systematic review and meta–analysis. BMC Cancer. 2016; 16: 1–13.

[28] Li J, Thompson T, Joseph DA, Master VA. Association between smoking status, and free, total and percent free prostate specific antigen. The Journal of Urology. 2012; 187: 1228-1233.

[29] Kristal AR, Chi C, Tangen CM, Goodman PJ, Etzioni R, Thompson IM. Associations of demographic and lifestyle characteristics with prostate-specific antigen (PSA) concentration and rate of PSA increase. Cancer. 2006; 106: 320–328.

[30] Gelmann EP, Chia D, Pinsky PF et al. Relationship of demographic and clinical factors to free and total prostate-specific antigen. Urology. 2001; 58: 561–566.

[31] Field AE, Colditz GA, Willett WC, Longcope C, McKinlay JB. The relation of smoking, age, relative weight, and dietary intake to serum adrenal steroids, sex hormones, and sex hormone-binding globulin in middle-aged men. The Journal of Clinical Endocrinology and Metabolism. 1994; 79: 1310–1316.

[32] Koc G, Akgul K, Yilmaz Y, Dirik A, Un S. The effects of cigarette smoking on prostate-specific antigen in two different age groups. Canadian Urological Association Journal. 2013; 7: E704.

[33] Moreira DM, Nickel JC, Gerber L, et al. Smoking Is Associated with Acute and Chronic Prostatic Inflammation: Results from the REDUCE study. Cancer Prevention Research. 2015; 8: 312–317.