



# The Relationships between Thyroid Hormone Levels and Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia

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**Purpose:** We examined the association between thyroid hormone and lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH).

**Materials and Methods:** A total of 5,708 middle aged men were included. LUTS/BPH were assessed using the international prostate symptom score (IPSS), total prostate volume (TPV), maximal flow rate (Q<sub>max</sub>), and a full metabolic workup. Thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels were measured using chemiluminescence immunoassay. We divided participants into quartiles based on their TSH and FT4 levels: first to fourth quartile (Q1–Q4).

**Results:** There was a significant increase in the percentage of men with IPSS>7, Q<sub>max</sub><10 mL/s, and TPV≥30 mL with increase of FT4 quartile. The adjusted odds ratio (OR) for TPV≥30 mL and IPSS>7 were significantly different between FT4 quartile groups (ORs; [5–95 percentile interval], p; TPV≥30 mL, Q1: 0.000 [references]; Q2: 1.140 [0.911–1.361], p=0.291; Q3: 1.260 [1.030–1.541], p=0.025; Q4: 1.367 [1.122–1.665], p=0.002; IPSS>7: Q1: 0.000 [references]; Q2: 0.969 [0.836–1.123], p=0.677; Q3: 1.123 [0.965–1.308], p=0.133; Q4: 1.221 [1.049–1.420], p=0.010). In men with above median levels of testosterone, the FT4 correlated positively with TPV, even after adjusting for confounders. However, the FT4 was not correlated with TPV in men with below median levels of testosterone. TSH was not related to LUTS/BPH measurements.

**Conclusions:** TPV, IPSS, and Q<sub>max</sub> were significantly related to FT4. TPV and IPSS were significantly and independently related to FT4. Additionally, the relationship between FT4 and TPV was distinct when testosterone levels are high.

**Keywords:** Prostate; Prostatic hyperplasia; Testosterone; Thyroid; Urinary tract diseases

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## INTRODUCTION

Benign prostatic hyperplasia (BPH) is highly prevalent in older men and increases with age [1]. In spite of extensive research efforts, the etiology of BPH has not been fully established. BPH might be caused by many

factors, including inflammation, metabolic syndrome (MetS), and endocrine hormones. In terms of endocrine factors, the roles of testosterone, estrogen, and growth factor have been reported [2]. However, scant data concerning the relationships between thyroid hormone and BPH are available.

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Investigational data have shown that thyroid hormones have a role in cell differentiation and growth as well as metabolism [3]. Recent clinical data reported that an increase in thyroid hormone is related to various cancers, including prostate cancer [4]. Additionally, some benign neoplasms are related to thyroid disease [5,6]. The possible relationships between thyroid hormone and BPH could be inferred from previous accumulated data. Therefore, we investigated the relationship between thyroid hormone and BPH in middle aged men to better understand the etiology of BPH. Additionally, we examine the role of testosterone in the relationships between thyroid hormone and BPH because testosterone is fundamental for developing BPH.

## **MATERIALS AND METHODS**

### **1. Subjects and ethics statement**

From September 2012 to November 2013, 5,708 men over 40 years of age received routine health check-ups at the Health Promotion Center of the National Police Hospital (Seoul, Korea). All of the participants provided written informed consent, and data concerning the participants were collected prospectively. The Institutional Review Board (IRB) of National Police Hospital approved this study (IRB number: 11100176-201611-HR-011).

### **2. Lower urinary tract symptoms/benign prostatic hyperplasia assessments**

The validated Korean version of international prostate symptom score (IPSS) was used. We divided participants into two categories: mild lower urinary tract symptoms (LUTS) (IPSS $\leq$ 7) and moderate to severe LUTS (IPSS $>$ 7).

The maximal flow rate (Q<sub>max</sub>) and postvoid residual urine volume (PVR) were assessed by uroflowmetry (Medtronic Inc., Minneapolis, MN, USA) and transabdominal ultrasonography (UltraView 800; BK Medical, Herlev, Denmark), respectively. If voided volume during uroflowmetry was less than 150 mL [7], we omitted the data of Q<sub>max</sub> and PVR. We divided participant according to Q<sub>max</sub> of 10 mL/s [7] or PVR of 50 mL [7], because Q<sub>max</sub> $<$ 10 mL/s or PVR $\geq$ 50 mL is significantly related to bladder outlet obstruction [7].

Total prostate volume (TPV) was calculated using transrectal ultrasonography (UltraView 800; BK Medi-

cal). TPV measurements were performed by a single sonographer. We calculated TPV according to previous methods [8]. We divided the participants according to TPV of 30 mL, because TPV $\geq$ 30 mL [9-11] is used in previous BPH epidemiologic studies.

In terms of prostate-specific antigen (PSA), we divided the participants according to PSA of 1.5 ng/mL, because PSA of  $>$ 1.5 ng/mL is significantly related to bladder outlet obstruction [12].

### **3. Metabolic syndrome assessment**

Two blood-pressure (mmHg) measurements, obtained 5 minutes apart using a mercury sphygmomanometer on the right arm, were averaged. Waist circumference (cm), to the nearest 0.1 cm, was measured midway between the lowest rib and the iliac crest. Body weight (kg) and body height (cm) were also recorded. Serum was collected in the morning (between 7:00 and 9:00 AM) after an overnight fast. The biochemical analyses performed measured fasting serum glucose level, triglyceride level, and high-density lipoprotein cholesterol level. A diagnosis of MetS required the satisfaction of three or more of the NCEP-ATP III criteria [13].

### **4. Hormonal assay**

Serum testosterone was measured via radioimmunoassay using a kit from Cisbio Bioassays, Inc. (Codolet, France). The intra-assay coefficients of variation for all assays were less than 9%, and the inter-assay coefficients of variation were less than 12%. For each assay, all samples from each subject were measured in the same assay run.

Free thyroxine (FT4) and thyroid-stimulating hormone (TSH) were estimated by chemiluminescence (Advia Centaur CP, Erlangen, Germany) using reagent kits from Siemens Diagnostic (Erlangen, Germany). The intra-assay coefficients of variation for all assays were less than 9%, and the inter-assay coefficients of variation were less than 12%.

### **5. Statistical analysis**

We excluded 126 men for whom testosterone, FT4, TSH, IPSS, uroflowmetry, body mass index, or TPV data were missing; men who had been administered related drugs including alpha blockers, phosphodiesterase-5 inhibitors, anti-psychotics, thyroid supplements or anti-thyroid drugs, steroids, or beta-blockers; men who had undergone surgery or had been hospitalized due to

trauma in last 3 months; and men with pyuria.

We divided participants into quartiles based on their TSH and FT4 measurements. TSH: first quartile (Q1) ( $\leq 0.96$  ng/mL); second quartile (Q2) ( $>0.96, \leq 1.44$  ng/mL); third quartile (Q3) ( $>1.44, \leq 2.1325$  ng/mL); and fourth quartile (Q4) ( $>2.1325$  ng/mL). FT4: Q1 ( $\leq 0.97$  ng/mL), Q2 ( $>0.97, \leq 1.05$  ng/mL), Q3 ( $>1.05, \leq 1.13$  ng/mL), and Q4 ( $>1.13$  ng/mL). We also divided participants into two groups based on their median testosterone level: testosterone  $\leq 5.06$  ng/mL and testosterone  $>5.06$  mL.

First, we evaluated whether the ratio of IPSS $>7$ , Qmax $<10$  mL/s, TPV $\geq 30$  mL, PVR $\geq 50$  mL, and PSA $>1.5$  ng/mL increased as FT4 or TSH quartile increased, using the Cochran-Armitage trend test (testing for the presence of a trend in case control or cross sectional studies where a series of increasing or decreasing exposures is being studied).

Second, the adjusted odds ratios (ORs) for IPSS $>7$ , Qmax $<10$  mL/s, TPV $\geq 30$  mL, PVR $\geq 50$  mL, and PSA $>1.5$  ng/mL in relation to FT4 or TSH quartile were calculated using logistic regression.

Third, we analyzed the trend of the ratio of TPV $\geq 30$  mL according to testosterone level to examine the impact of testosterone level (testosterone  $\leq 5.06$  ng/mL and testosterone  $>5.06$  mL) on the relationship between thyroid hormone and TPV using the Cochran-Armitage trend test. Additionally, adjusted ORs for TPV $\geq 30$  mL in relation to FT4 quartile were calculated according to testosterone level (testosterone  $\leq 5.06$  ng/mL and testosterone  $>5.06$  mL) to confirm the impact of testosterone level on the relationship between thyroid hormone and TPV after adjustment.

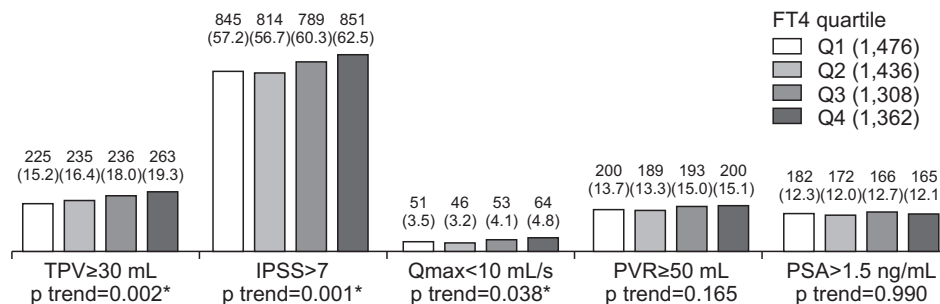
All tests were two-sided, with statistical significance set at  $p < 0.05$ . Analyses were conducted with the R sta-

**Table 1.** Participants' characteristics (n=5,582)

Variable	Value
Age (y)	51.1 $\pm$ 5.2
BMI (kg/m <sup>2</sup> )	25.0 $\pm$ 2.4
No. of MetS component	
0	675 (12.1)
1	1,188 (21.3)
2	1,381 (24.7)
3	1,293 (23.2)
4	827 (14.8)
5	218 (3.9)
FT4 (ng/dL)	1.05 $\pm$ 0.14
TSH (ng/dL)	1.44 (0.96–2.13)
TPV (mL)	
<20	1,481 (26.5)
20–29	3,142 (56.3)
30–39	770 (13.8)
$\geq 40$	189 (3.4)
Uroflowmetry	
Voided volume (mL)	354.0 (244.0–486.0)
Qmax	
<15 mL/s	1,097 (19.7)
<10 mL/s	214 (3.8)
PVR $\geq 50$ mL	782 (14.0)
PSA	0.71 (0.048–1.08)
IPSS	
Mild LUTS	2,283 (40.9)
Moderate LUTS	2,612 (46.8)
Severe LUTS	687 (12.3)
Testosterone (ng/mL)	5.2 $\pm$ 1.5

Values are presented as mean $\pm$ standard deviation, number (%), or median (interquartile range).

BMI: body mass index, MetS: metabolic syndrome, FT4: free thyroxine, TSH: thyroid stimulating hormone, TPV: total prostate volume, Qmax: maximal flow rate, PVR: postvoid residual urine volume, PSA: prostate specific antigen, IPSS: international prostate symptom score, LUTS: lower urinary tract symptoms.



**Fig. 1.** Relationships between FT4 and LUTS/BPH measurements. Values are presented as number (%). Cochran-Armitage trend test were used for statistical analysis. FT4: free thyroxine, LUTS: lower urinary tract symptoms, BPH: benign prostatic hyperplasia, TPV: total prostate volume, IPSS: international prostate symptom score, Qmax: maximal flow rate, PVR: postvoid residual urine volume, PSA: prostate specific antigen, Q1: first quartile, Q2: second quartile, Q3: third quartile, Q4: fourth quartile. \*p-value statistically significant  $< 0.05$ .

tistical package v.2.13.1 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### 1. Patient characteristics

The characteristics of the patient population are shown in Table 1. Mean TPV, IPSS, and Qmax was 24.1±7.0 mL, 10.6±7.1, and 23.0±8.6 mL/s, respectively. In addition, the ratio of MetS was 41.9%, and the median PVR (interquartile range) was 0 mL (0–38.0 mL).

### 2. Free thyroxine and lower urinary tract symptoms/benign prostatic hyperplasia

There was a significant increase in the percentage of men with IPSS>7, Qmax<10 mL/s, and TPV≥30 mL with increase in FT4 quartile, but not PVR≥50 mL and PSA>1.5 ng/mL (Fig. 1). After adjusting, the ORs for TPV≥30 mL of FT4 Q3 and FT4 Q4 were significantly higher than FT4 Q1 (Table 2). Additionally, the adjusted ORs for IPSS>7 of FT4 Q4 were significantly higher than that of FT4 Q1 (Table 2). However, the adjusted ORs for Qmax<10 mL/s, PVR≥50 mL, and PSA>1.5 ng/mL were not significantly different between FT4 quartile groups (Table 2). In sum, IPSS, Qmax, and TPV were significantly related to FT4, and IPSS. In addition, TPV were significantly and independently related to FT4.

### 3. Thyroid-stimulating hormone and lower urinary tract symptoms/benign prostatic hyperplasia

TSH was not significantly related to IPSS, TPV, Qmax, PVR, or PSA in univariate and multivariate analysis (Fig. 2, Table 3).

### 4. Impact of testosterone level on the relationship between free thyroxine and total prostate volume

TPV among LUTS/BPH measurements was most related to FT4 in this study (smallest p-value), and prostate enlargement is one of the most important components of LUTS/BPH development. And, testosterone is fundamental for developing LUTS/BPH. Therefore, we examined whether the relationship between FT4 and TPV is maintained after subgroup analysis according to testosterone level. In high testosterone levels (testosterone>5.06 mL), the percentage of men with TPV≥30

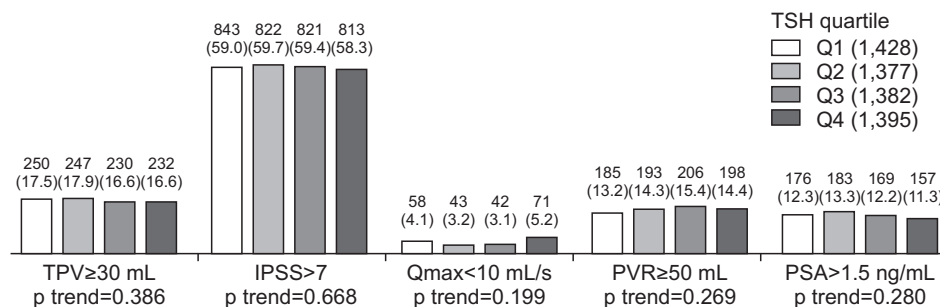
Table 2. Adjusted ORs of FT4 for LUTS/BPH measurement

FT4	TPV≥30 mL <sup>a</sup>		IPSS>7 <sup>b</sup>		Qmax<10 mL/sec <sup>c</sup>		PVR≥50 mL <sup>c</sup>		PSA>1.5 ng/mL <sup>b</sup>	
	ORs	p-value <sup>d</sup>	ORs	p-value <sup>d</sup>	ORs	p-value <sup>d</sup>	ORs	p-value <sup>d</sup>	ORs	p-value <sup>d</sup>
Q1	1.000 (references)		1.000 (references)		1.000 (references)		1.000 (references)		1.000 (references)	
Q2	1.113 (0.910–1.361)	0.296	0.970 (0.837–1.124)	0.684	0.890 (0.592–1.338)	0.576	0.970 (0.782–1.203)	0.779	0.967 (0.773–1.210)	0.770
Q3	1.256 (1.027–1.537)	0.027*	1.121 (0.963–1.305)	0.141	1.145 (0.772–1.698)	0.500	1.097 (0.885–1.361)	0.398	1.056 (0.842–1.324)	0.638
Q4	1.364 (1.120–1.662)	0.002*	1.215 (1.044–1.414)	0.012*	1.340 (0.918–1.955)	0.129	1.092 (0.882–1.353)	0.419	0.990 (0.789–1.242)	0.932

Values are presented as adjusted ORs (5%–95% confidence interval).

ORs: odds ratios; FT4: free thyroxine, LUTS: lower urinary tract symptoms, BPH: benign prostatic hyperplasia, TPV: total prostate volume, IPSS: international prostate symptom score, Qmax: maximal flow rate, PVR: postvoid residual urine volume, PSA: prostate-specific antigen, Q1: first quartile, Q2: second quartile, Q3: third quartile, Q4: fourth quartile.

<sup>a</sup>Adjusted for age, body mass index (BMI), testosterone level, and number of metabolic syndrome components. <sup>b</sup>Adjusted for age, BMI, testosterone level, number of metabolic syndrome components, and total prostate volume. <sup>c</sup>Adjusted for age, BMI, testosterone level, number of metabolic syndrome components, total prostate volume, and voided volume during uroflowmetry. <sup>d</sup>Logistic regression analysis. \*p-value statistically significant <0.05.



**Fig. 2.** Relationships between TSH and LUTS/BPH measurements. Values are presented as number (%). Cochran-Armitage trend test were used for statistical analysis. TSH: thyroid stimulating hormone, LUTS: lower urinary tract symptoms, BPH: benign prostatic hyperplasia, TPV: total prostate volume, IPSS: international prostate symptom score, Qmax: maximal flow rate, PVR: postvoid residual urine volume, PSA: prostate specific antigen, Q1: first quartile, Q2: second quartile, Q3: third quartile, Q4: fourth quartile.

mL significantly increased with an increase of FT4 quartile, but not in low testosterone levels (testosterone  $\leq 5.06$  ng/mL) (Table 4). The relationship between TPV  $\geq 30$  mL and FT4 in high testosterone levels was maintained after adjusting for confounding factors (Table 5), but not in the low testosterone level. According to our results, the relationship between FT4 and TPV was distinct only in high testosterone levels.

## DISCUSSION

In this study, TPV, IPSS, and Qmax were significantly related to FT4 in univariate analysis. Additionally, TPV and IPSS were significantly related to FT4 in multivariate analysis. However, TSH was not related to LUTS/BPH measurements.

BPH is induced by static and/or dynamic pathways [14]. According to this theory, the dynamic component of bladder outlet obstruction was induced by the tension of prostate smooth muscle by increased alpha-adrenoceptors. The static component of bladder outlet obstruction was induced by the anatomic obstruction resulting from enlargement of the prostate.

In terms of static components, previous data showed the relationship between thyroid hormone levels and prostate enlargement. A case-control study [15] (including 20 BPH cases and 27 normal controls) from the USA reported that mean tri-iodothyronine was higher in BPH cases compared to controls ( $72.0 \pm 24.9$  ng/dL vs.  $94.4 \pm 12.3$  ng/dL,  $p < 0.001$ ). However, the data concerning exact prostate size was missing in this data [15]. A case-control study [16] (including 40 BPH cases and 40 normal controls) conducted in India showed that free tri-iodothyronine and FT4 were significantly higher

in BPH cases (median TPV: 45.5 mL) when compared with normal controls (median TPV: 18 mL). However, the Indian data had few participants and did not adjust for confounding factors, such as age, testosterone level, and MetS, which are very important factors in developing BPH. In our data including a large population of middle-aged men, TPV was related to FT4 throughout the statistical analyses, including univariate and multivariate analyses. Our data confirm the significant and independent relationship between thyroid hormone and prostate enlargement in more precise ways than any other study. Therefore, our results suggest a possible role of FT4 in the development of LUTS/BPH.

The mechanism of the relationship between thyroid hormone and prostate enlargement is unclear [16]. Some type of mechanism connecting thyroid hormone and cancer could be applied to our results [16]. There are several pathways that may explain the relationship between cancer and thyroid function, as follow [17]: first, the binding of thyroid hormone to thyroid hormone receptors initiates the oncogenic phosphatidylinositol-3-kinase (PI3K) pathway [4,17], then the PI3K pathway induces the expression of transcription factor hypoxia-inducible factor 1 (HIF1). HIF1 target genes induce tumor development, growth, invasion and metastasis. Second, thyroid hormone binds to the protein integrin  $\alpha v \beta 3$ . This binding leads to activation of the PI3K and ERK1/2 pathways. The latter pathway induces fibroblast growth factor 2, which is a stimulator of angiogenesis [4,17]. In addition, thyroid hormone activates mitogen-activated protein kinase (MAPK) [17,18]. MAPK induces the serine phosphorylation of thyroid receptors, which induces angiogenesis

**Table 3.** Adjusted ORs of TSH for LUTS/BPH measurement

TSH	TPV≥30 mL <sup>a</sup>		IPSS>7 <sup>b</sup>		Qmax<10 mL/s <sup>c</sup>		PVR≥50 mL <sup>c</sup>		PSA>1.5 ng/mL <sup>b</sup>	
	ORs	p-value <sup>d</sup>	ORs	p-value <sup>d</sup>	ORs	p-value <sup>d</sup>	ORs	p-value <sup>d</sup>	ORs	p-value <sup>d</sup>
Q1	1.000 (references)		1.000 (references)		1.000 (references)		1.000 (references)		1.000 (references)	
Q2	1.013 (0.833–1.231)	0.901	1.037 (0.891–1.206)	0.639	0.773 (0.517–1.158)	0.212	1.097 (0.881–1.365)	0.409	1.090 (0.872–1.362)	0.450
Q3	0.928 (0.761–1.132)	0.461	1.021 (0.877–1.187)	0.792	0.752 (0.501–1.129)	0.169	1.174 (0.946–1.457)	0.146	0.983 (0.783–1.232)	0.880
Q4	0.937 (0.769–1.142)	0.521	0.985 (0.848–1.145)	0.846	1.314 (0.919–1.879)	0.135	1.143 (0.919–1.421)	0.229	0.881 (0.700–1.110)	0.283

Values are presented as adjusted ORs (5%–95% confidence interval).

ORs: odds ratios, TSH: thyroid-stimulating hormone, LUTS: lower urinary tract symptoms, BPH: benign prostatic hyperplasia, TPV: total prostate volume, IPSS: international prostate symptom score, Qmax: maximal flow rate, PVR: postvoid residual urine volume, PSA: prostate-specific antigen, Q1: first quartile, Q2: second quartile, Q3: third quartile, Q4: fourth quartile.

<sup>a</sup>Adjusted for age, body mass index (BMI), testosterone level, and number of metabolic syndrome components. <sup>b</sup>Adjusted for age, BMI, testosterone level, number of metabolic syndrome components, and total prostate volume. <sup>c</sup>Adjusted for age, BMI, testosterone level, number of metabolic syndrome components, total prostate volume, and voided volume during uroflowmetry. <sup>d</sup>Logistic regression analysis.

**Table 4.** Relationships between FT4 and TPV ≥30 mL according to testosterone level

Testosterone level	FT4				p-value <sup>a</sup>
	Q1	Q2	Q3	Q4	
≤5.06 ng/mL	16.6	14.8	18.4	18.2	0.189
>5.06 ng/mL	13.9	18.0	17.7	20.5	0.002*

Values are presented as percent only.

FT4: free thyroxine, TPV: total prostate volume, Q1: first quartile, Q2: second quartile, Q3: third quartile, Q4: fourth quartile.

<sup>a</sup>Cochran-Armitage trend test. \*p-value statistically significant <0.05.

**Table 5.** Adjusted ORs of FT4 for TPV ≥30 mL<sup>a</sup> according to testosterone level

Testosterone level	FT4	Adjusted ORs (5%–95% confidence interval)	p-value <sup>b</sup>
≤5.06 ng/mL	Q1	1.000 (references)	
	Q2	0.883 (0.663–1.175)	0.393
	Q3	1.145 (0.864–1.516)	0.345
	Q4	1.222 (0.851–1.481)	0.414
>5.06 ng/mL	Q1	1.000 (references)	
	Q2	1.394 (1.050–1.851)	0.022*
	Q3	1.386 (1.036–1.852)	0.028*
	Q4	1.661 (1.253–2.203)	<0.001*

ORs: odds ratios, FT4: free thyroxine, TPV: total prostate volume, Q1: first quartile, Q2: second quartile, Q3: third quartile, Q4: fourth quartile.

<sup>a</sup>Adjusted for age, body mass index, and number of metabolic syndrome components. <sup>b</sup>Logistic regression analysis. \*p-value statistically significant <0.05.

and tumor proliferation [17,18]. Further investigational research is needed to identify the exact mechanism in the relation between prostate enlargement and thyroid function.

In contrast to FT4, TSH is not clearly correlated with LUTS/BPH measurements. However, TSH was related to prostate size in previous data from India [16]. Approximately 85% of thyroid hormone produced in the body is T4. The 99.8% of thyroid hormones are protein-bound, and only the free components, including FT4 have the ability to bind to their respective receptors. TSH, which is released from the pituitary gland, regulates the production of thyroid hormone, but TSH itself does not act as thyroid hormone. Therefore, FT4 is more representative of thyroid function rather than TSH. Considering the aforementioned issues, our results showing that TSH is not related to LUTS/BPH measurements does not hinder the fact that thyroid function is related to LUTS/BPH.

In this study, the relationship between FT4 and

TPV was maintained only in high testosterone levels. Similar results have been reported in the relationship between estrogen and BPH. In the Olmsted County cohort [19], in men with above median levels of testosterone, the estradiol level correlated positively with TPV. In dogs, treatment of castrated male dogs with androgens and estrogens led to more extensive prostate enlargement than androgen or estrogen single treatment [20]. Therefore, it has been suggested that androgens may serve as a potential “pool” for metabolism to estrogens that can promote or inhibit prostatic proliferation [21]. We speculate that androgens may also serve as a potential “pool” for metabolism to thyroid hormone.

Several limitations of the present study warrant discussion. First, the cross-sectional nature of the dataset makes causal inferences problematic. In addition, there may be a potential selection bias because our data are from a single institution. However, we think that our data are highly relevant because this study was a large cross-sectional study.

## CONCLUSIONS

In summary, TPV, IPSS, and Qmax were significantly related to FT4. TPV and IPSS were significantly and independently related to FT4. Additionally, the relationship between FT4 and TPV is distinct when testosterone levels are high. We found a possible role of thyroid hormone in the development of LUTS/BPH, and we demonstrated a possible role of testosterone in the relationship between thyroid hormone and TPV.

## Disclosure

The authors have no potential conflicts of interest to disclose.

## Author Contribution

Lee JH conceived of the study, drafted the manuscript, and performed the statistical analysis. Park YW participated in data collection. Lee SW participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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