Transrectal Ultrasound (TRUS) Findings of the Prostate Gland in Late Onset Hypogonadism with Testosterone Supplementation in Correlation with Clinical Outcome

Sith Phongkitkarun MD*,
Apinan Rassameepong MD*, Sompol Permpongkosol MD, PhD**,
Mayureewan Taphey MD*, Bussanee Wibulpolprasert MD*

* Department of Radiology, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand
** Department of Surgery, Faculty of Medicine, Ramathibodi Hospital Bangkok, Thailand

Objective: To determine the TRUS findings of the prostate and correlation of ultrasound findings with clinical outcomes in late-onset hypogonadal (LOH) men with testosterone supplementation.

Material and Method: Between January 2007 and September 2010, TRUS findings and clinical outcomes of 16 from 226 subjects were studied. The demographic data, ultrasound parameters as prostate volume and vascularity, and clinical parameters were evaluated. Correlation between ultrasound and clinical parameters were analyzed using Pearson correlation analysis.

Results: During mean time follow-up of 6.48 months, the volume of the central gland (CG) significantly increased (p = 0.02), the volume of the total gland (TG) increased, and the volume of the peripheral zone (PZ) slightly decreased. The vascularity of the TG, CG, and PZ were significantly increased. The periurethral region vascularity was not significantly increased (p = 0.06), whereas total serum testosterone, prostate specific antigen (PSA), and PSA density were increased. The International Prostate Symptom Score (IPSS) was significantly decreased (p < 0.001). There was a significant correlation between increased prostate volume and increased serum PSA.

Conclusion: Testosterone supplementation in LOH men was found to cause an increase in TG volume during the first six months. The preferentially increased CG volume and prostatic vascularity might be due to exogenous testosterone. The authors observed a significantly increased PSA with a strong correlation between serum PSA and prostate volume.

Keywords: Prostate, Transrectal ultrasound, Late onset hypogonadism, Testosterone supplementation

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At present, prior to initiation of testosterone supplementation all patients should be excluded from the condition of prostate cancer by undergoing digital examination, measuring serum PSA, or ultrasound (US) of the prostate[1-3,7,9]. During treatment, the patient who undergoes testosterone supplementation should be monitored for the clinical outcome of prostate disease at three, six, and 12 months, and at least annually thereafter[2].

Transrectal ultrasound (TRUS) of the prostate is a diagnostic modality that has become useful in determining prostate lesions of BPH, prostatitis, obstructive infertility, and prostate cancer[9]. However, TRUS findings of the prostate after testosterone supplementation have not yet been well described.

The aim of the present study was to determine the findings of transrectal ultrasound of the prostate particular prostate vascularity and the correlation of
ultrasound findings with clinical outcome in late-onset hypogonadal men with testosterone supplementation.

**Material and Method**

**Patients**

A retrospective review of medical records of all men with diagnosis of late onset hypogonadism (LOH) who had been treated with long acting testosterone undecanoate between January 2007 and September 2010 revealed 226 subjects. The inclusion criteria included LOH men who had TRUS performed before testosterone supplementation and had at least one follow-up TRUS. Therefore, 119 subjects who had transrectal ultrasound (TRUS) performed less than two examinations and 91 subjects who had first TRUS performed after starting testosterone supplementation were excluded. The remaining 16 subjects were left in the present study. The present study was conducted with the approval of the Institutional Review Board and a waiver of patient informed consent because it was a retrospective study.

All of the included subjects were treated with parenteral testosterone at Men’s Health Clinic, Ramathibodi Hospital. Injections of testosterone undecanoate (1,000 mg) were given at 0, 6 weeks, and every 12 weeks without dose adjustment according to protocols.

**Sonographic examination**

**Transrectal ultrasound (TRUS) examination technique**

The transrectal ultrasound examination of prostate was performed by one of three radiologists using a transrectal sonographic 5-9 MHz probe and Philips IU 22 system (Bothell WA, 98041 USA).

**Scanning technique**

The patient lay on left lateral decubitus position. The digital rectal examination was performed before probe insertion to detect rectal abnormalities. The probe was covered with condom coated outside with sonographic gel.

The probe was inserted into the rectum. First, both seminal vesicles were evaluated in transverse plane at just above the prostate base. Then, the base of prostate gland, peripheral zone, central zone, transitional zone, and fibromuscular stroma were evaluated in the transverse plane. The abnormalities were recorded.

Continuously, the prostate gland was surveyed from right side to midline to left side, by rotating the probe to the sagittal plane. The prostate volume was determined with formula: length x height x width x 0.52. The length was measured as greatest dimension in the sagittal plane, then the height (AP) was measured as perpendicular dimension in the length, and the width was measured as greatest dimension in the transverse plane of both total and central prostate volume. The central gland volume includes the anatomical regions of central zone, transitional zone, and anterior fibromuscular stroma. The peripheral zone volume was calculated by the difference between total prostate volume and central gland volume.

Power Doppler ultrasound was performed to evaluate prostate vascularity in all patients. The optimized detection of low-velocity flow was performed by setting the repetition frequency ranging from 500 to 700 Hz and a wall filter of 42-46 Hz.

**Semi-quantitative measurement of prostate vascularity**

Prostate vascularity was calculated by using the ImageJ that is a public domain, Java-base image processing program developed at the National Institutes of Health (agency of the United States Department of Health and Human Services). The vascularity of the total prostate, peripheral zone, central gland (including central zone, transitional zone, and anterior fibromuscular stroma) and periurethral region were calculated by drawing region of interest (ROI). The three images of each total prostate, peripheral zone and central gland were selected. The average pixel counts of three regions (total prostate, peripheral zone and central gland) as well as the periurethral region were calculated into percentage of vascularity pixels compared to the non-vasculatity background pixels (Fig. 1).

**Clinical evaluation**

All included patients were evaluated clinically by using total serum testosterone, serum PSA, PSA density and the International Prostate Symptom Score (IPSS). The total serum testosterone was measured by commercial chemiluminescence kit (Immufite, Siemens Healthcare Diagnostics, USA). The PSA density was calculated by PSA/total prostate volume and IPSS was obtained by using IPSS questionnaire. The IPSS scores are from 0 (no complaints) to 5 (almost always) that cumulative scores of all seven questions with maximum score of 35.

**Statistical analysis**

Continuous variables were summarized as mean (SD) or median (range). Categorical variables
were summarized as counts and percentage. Statistical
difference of ultrasound findings and clinical outcomes
in before and after treatment was analyzed using
paired-samples t-test. Pearson correlation coefficient
was used to determine the relationship between
ultrasound findings and clinical outcomes. All p-values
were two-sided and \( p < 0.05 \) was considered statistical
significance. All statistical calculations were done
using SPSS computer package version 17.0 (SPSS Inc.,
Chicago, IL, USA).

Results

The population consisted of 16 patients
with mean age \( 67.11 \pm 10.16 \) years. Fourteen patients
\( (87.5\%) \) had BPH, five \( (31.3\%) \) had diabetes mellitus,
ine \( (56.3\%) \) had hypertension, eight \( (50.0\%) \) had
erectile dysfunction, and two \( (12.5\%) \) had lower
urinary tract symptoms (LUTS).

Nine patients had been treated with \( \alpha_1 \)
adrenergic receptor antagonist, seven patients \( (77.78\%) \)
had BPH, and two patients \( (22.22\%) \) had LUTS.

Seven patients had prostatic lesions at the
baseline transrectal ultrasound (TRUS), in which, one
lesion was pathologically proven of BPH, two were
confirmed fibrosis on MRI examination, and four were
unchanged after follow-up ultrasound and diagnosed
as fibrosis or prostatitis and hyperplastic nodule. None
had prostatic malignancy or new nodule on TRUS.

Seven patients had serum PSA more than
4 ng/ml, from which five had initial serum PSA more
than 4 ng/ml before testosterone supplementation and
two had serum PSA rising during testosterone
supplementation. Five patients underwent prostatic
transrectal ultrasound biopsy and pathological
diagnosis of all of them showed benign prostatic
hyperplasia. Two patients did not have prostatic biopsy
performed, but they underwent MRI examination of
prostate gland. One patient showed area of fibrosis or
focal prostatitis at peripheral zone and one showed
suspected small prostate cancer.

After testosterone supplementation, there was
a significantly increased central gland volume, but not
significantly increased total prostate gland volume. The
peripheral zone volume was slightly decreased. The
vascularity of the total prostate, central gland and
peripheral zone were significantly increased. The periurethral region vascularity was not significantly
increased \( (p = 0.06) \), whereas total serum testosterone,
prostate specific antigen (PSA) and PSA density were
increased. However, the international prostate symptom
score was significantly decreased (Table 1).

The follow-up time was categorized into
three periods as less than four months, between four
and 12 months, and more than 12 months (Table 2).

The central gland volume was preferentially
increased during all three periods of TRUS follow-up.
All zonal prostate vascularity (total prostate, central
gland, peripheral zone and periurethral region) were
also increased during these three periods. The total
prostate vascularity was also significantly increased.
The serum testosterone was significantly increased
during the testosterone supplementation, while the
IPSS was decreased. The serum PSA was also increased
during all periods of TRUS follow-up.

There was a significant correlation between
increased prostate volume and increased serum PSA
after testosterone supplementation \( (p < 0.001) \).

After testosterone supplementation, there had
a significant decrease of IPSS in both groups of patients
who was received or did not receive \( \alpha_1 \)-adrenergic
antagonist (Table 3).

Discussion

The present study demonstrates that the
changes of prostate after testosterone supplementation
could be seen by transrectal ultrasound technique. It
appears that there were significantly increased central
gland volume and prostate vascularity.

The study by Minnemann et al\(^{[10]}\) has shown
a significantly increased prostate volume in the first
12 months of the 25 men with parenteral testosterone

![Measurement of prostate vascularity by pixel count analysis using Image J post-processing software](image.jpg)
undecanoate supplementation. Snyder et al (5) found a dramatically increased prostate volume during the first six months of testosterone supplementation and it was still significantly increased at 36 months of testosterone treatment. These two studies rendered support to the present results, which showed an increased prostate volume, particularly central gland volume, after testosterone supplementation.

Although the study by Emmelot-Vonk et al (11) did not show any significant change in prostate volume in the testosterone supplementation group compared with the placebo group. The present study also revealed an increased prostate volume during six months when compared to the base line.

In addition, the increased central gland volume was preferentially more than other prostatic zones during all three periods of TRUS follow-up. To the authors’ knowledge, this is the first study that evaluates prostate zonal volume by dividing it into three zonal volumes (total prostate, central gland, and peripheral zone) in the late onset hypogonadal men with testosterone supplementation.

Two studies performed by Liu et al (12) and Schatzl et al (13) found two etiologic factors of BPH, including age and androgen status, from which age is the most common risk factor. Androgen has been well accepted as the second risk factor. BPH is the condition that has been described by an increase in the cellular content of the transitional zone located in the central gland (9). It was not that most patients in the present study (87.5%) already had some degree of BPH before testosterone supplementation. The authors believe that preferentially increased of central gland volume in the present study may be due to add on BPH condition as a result of exogenous testosterone from supplementation.

There were nine patients (56.3%) in the present study who received α1-adrenergic receptor antagonist to treat obstructive symptom of BPH by relaxing smooth muscle in the prostate and the bladder neck, thus decreasing the blockage of the urine flow. The present study found that both treated and untreated groups with α1-adrenergic receptor antagonist revealed a significant decrease of IPSS representing lower urinary tract symptoms. Two studies by Permpongkosol et al (14) and Haider et al (15) also reported the effect of testosterone replacement to improve LUTS and bladder function.

Table 1. Effect of testosterone supplementation on TRUS parameters and clinical parameters (n = 16 patients, mean time = 6.48 months)

<table>
<thead>
<tr>
<th>Ultrasound parameters</th>
<th>Mean (SD)</th>
<th>Change difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After treatment</td>
<td></td>
</tr>
<tr>
<td>Prostate volume (cc)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total prostate</td>
<td>40.49 (24.6)</td>
<td>41.73 (27.7)</td>
<td>1.23 (-3.53 to 6.01)</td>
</tr>
<tr>
<td>Central gland</td>
<td>18.80 (17.2)</td>
<td>21.50 (18.2)</td>
<td>2.68 (0.46 to 4.89)</td>
</tr>
<tr>
<td>Peripheral zone</td>
<td>21.67 (11.0)</td>
<td>20.23 (10.4)</td>
<td>-1.44 (-6.17 to 3.30)</td>
</tr>
<tr>
<td>Prostate vascularity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total prostate</td>
<td>7.35 (4.0)</td>
<td>15.47 (8.0)</td>
<td>8.13 (3.89 to 12.36)</td>
</tr>
<tr>
<td>Central gland</td>
<td>7.21 (5.0)</td>
<td>14.20 (8.8)</td>
<td>6.99 (2.88 to 11.09)</td>
</tr>
<tr>
<td>Peripheral zone</td>
<td>7.57 (4.1)</td>
<td>16.78 (11.2)</td>
<td>9.21 (3.41 to 15.02)</td>
</tr>
<tr>
<td>Periurethra region*</td>
<td>8.94 (12.23)</td>
<td>19.93 (7.84)</td>
<td>10.99 (-0.55 to 22.53)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Mean (SD)</th>
<th>Change difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (ng/dl)</td>
<td>257.06 (57.7)</td>
<td>574.19 (216.6)</td>
<td>317.13 (205.04 to 429.21)</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>2.72 (2.6)</td>
<td>3.14 (3.2)</td>
<td>0.42 (0.03 to 0.81)</td>
</tr>
<tr>
<td>PSA density</td>
<td>0.06 (0.04)</td>
<td>0.07 (0.05)</td>
<td>0.01 (-0.003 to 0.20)</td>
</tr>
<tr>
<td>IPSS</td>
<td>10.94 (7.1)</td>
<td>7.44 (5.7)</td>
<td>-3.50 (-5.16 to -1.84)</td>
</tr>
</tbody>
</table>

TRUS = transrectal ultrasound; CI = confidence interval; PSA = prostate specific antigen; IPSS = international prostate symptom score

* 10 patients were missing data
To the authors’ knowledge, there has been no study so far to explain the effect of exogenous testosterone on prostate vascularity. The present study is the first study that has evaluated prostatic vascularity in the late onset hypogonadal men with testosterone supplementation in pixel count percentage. The technique can provide prostate vascularity data in a quantitative manner. The present study found a significantly increased vascularity of total prostate, central gland, and peripheral zone after testosterone supplementation. The periurethral region also showed an increased vascularity, but it was not significantly

<table>
<thead>
<tr>
<th>Parameters</th>
<th>With α1-adrenergic antagonist (n = 9)</th>
<th>Without α1-adrenergic antagonist (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate volume (cc)</td>
<td>Mean change (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Total prostate</td>
<td>-0.71 (-7.43 to 6.02)</td>
<td>0.82</td>
</tr>
<tr>
<td>Central gland</td>
<td>3.24 (1.20 to 5.28)</td>
<td>0.01</td>
</tr>
<tr>
<td>Peripheral zone</td>
<td>-3.95 (-10.42 to 2.52)</td>
<td>0.20</td>
</tr>
<tr>
<td>Clinical parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>243.22 (144.2 to 341.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>0.43 (-0.20 to 1.06)</td>
<td>0.16</td>
</tr>
<tr>
<td>PSA density</td>
<td>0.01 (-0.008 to 0.03)</td>
<td>0.19</td>
</tr>
<tr>
<td>IPSS</td>
<td>-5.44 (-7.59 to -3.30)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval; PSA = prostate specific antigen; IPSS = international prostate symptom score

PSA = prostate specific antigen; IPSS = international prostate symptom score
* Statistically significant difference

Table 2. Effect of testosterone supplementation on TRUS parameters and clinical parameters categorized into three periods of follow-up

<table>
<thead>
<tr>
<th>Ultrasound parameters</th>
<th>Follow-up time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than 4 months</td>
</tr>
<tr>
<td></td>
<td>(n = 6)</td>
</tr>
<tr>
<td>Prostate volume (cc)</td>
<td></td>
</tr>
<tr>
<td>Total prostate</td>
<td>48.8</td>
</tr>
<tr>
<td>Central gland</td>
<td>26.3</td>
</tr>
<tr>
<td>Peripheral zone</td>
<td>22.6</td>
</tr>
<tr>
<td>Prostate vascularity (%)</td>
<td></td>
</tr>
<tr>
<td>Total prostate</td>
<td>4.9</td>
</tr>
<tr>
<td>Central gland</td>
<td>4.5</td>
</tr>
<tr>
<td>Peripheral zone</td>
<td>5.6</td>
</tr>
<tr>
<td>Periurethra region</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Table 3. Effect of testosterone supplementation on the prostate volume and clinical parameters in patients with or without α1-adrenergic antagonist treatment
different. This might be due to some missing data or low number of population. This result suggests that the testosterone supplementation causes increased prostatic vascularity. However, many conditions may give appearance of increased prostate vascularity such as prostatic malignancy, prostatitis, prostatic abscess, ejaculation within 24 hours, and BPH nodule in the transitional zone\(^{(16)}\). Additional study with a large population is needed to confirm these results.

After testosterone supplementation, serum PSA was significantly increased in the present study. However, it was not rising beyond the upper normal limit (4 ng/dl). This result was similar to the study of Gerstenbluth et al\(^{(17)}\) that showed a significantly increased serum PSA in hypogonadal men with testosterone supplementation. It may be due to the low PSA level in hypogonadal men that responded to normal level when receiving testosterone supplementation\(^{(18)}\). However, serum PSA can elevate in many conditions such as prostate cancer, BPH, inflammation, prostate manipulation, biopsy, and cystoscopy\(^{(9)}\).

In addition, the present results showed a significant correlation between increased total prostate volume, central gland volume and peripheral zone volume with increased serum PSA. The study by Roehrborn et al\(^{(19)}\) supported the present study and they showed a strong correlation between prostate volume and serum PSA level; this relationship also depends on age.

There are several limitations in the present study. First, there is small sample size. Second, the time of TRUS follow-up varies. Third, there is incomplete information of periurethral region vascularity. Fourth, due to the operator dependent nature of ultrasound, there are variations in how TRUS is performed among radiologist that may affect prostate volume measurement and vascularity.

In conclusion, testosterone supplementation in late onset hypogonadal men was found to cause increased total prostate volume during the first six months after testosterone supplementation. The preferentially increased central gland volume may be due to exogenous testosterone and underlying BPH condition. Increased prostatic vascularity may result from exogenous testosterone supplementation and should exclude pathologic conditions. Significant increased serum PSA and a strong correlation between increased prostate volume and increased serum PSA was observed.

Potential conflicts of interest

None.

References

12. Liu CC, Huang SP, Li WM, Wang CJ, Chou YH, Li CC, et al. Relationship between serum...

ผลของฮอร์โมนเทสโทสเตอโรนต่อต่อมลูกหมากในผู้ป่วยที่ขาดฮอร์โมนเทสโทสเตอโรน อาการตรวจ อัลตราซาวด์ของการตรวจต่อมลูกหมากทางทวารหนัก เปรียบเทียบกับข้อมูลทางคลินิก

สิทธิ์ พงษ์กิจกรุณ์, อภินันท์ รัศมีพงศ์, สมพล เพิ่มพงศ์โกศล, มยุรีวรรณ ตะเพย, บุษณี วิบุลผลประเสริฐ

วัตถุประสงค์: เพื่อศึกษาลักษณะการเปลี่ยนแปลงของต่อมลูกหมากด้วยการตรวจอัลตราซาวด์และการตรวจต่อมลูกหมากทางทวารหนัก ในผู้ป่วยที่ได้รับฮอร์โมนเทสโทสเตอโรน และวัดระดับฮอร์โมน เปรียบเทียบกับอาการทางคลินิก

วัตถุดิบและวิธีการ: เป็นการศึกษาย้อนหลังในผู้ป่วยที่ได้รับเทสโทสเตอโรน 16 คน ที่ได้ตรวจอัลตราซาวด์และการตรวจต่อมลูกหมาก ทั้งหมดหลังจากได้รับฮอร์โมน และทำการเปรียบเทียบระหว่างขนาดของต่อมลูกหมาก ปริมาณหลอดเลือดในต่อมลูกหมาก ค่าซีรัม PSA และการตรวจ IPSS (International Prostatic Symptom Score) และการวัดพิษมันฟันธdı์สี

ผลการศึกษา: พบว่าเมื่อได้รับฮอร์โมน ต่อมลูกหมากส่วน central gland มีขนาดเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ (p = 0.02) ในช่วงเวลาติดตามเฉลี่ยประมาณ 6 เดือนครึ่ง ส่วนรัศมีหลอดเลือดที่เข้าไปในต่อมลูกหมากในทุกส่วนของต่อมลูกหมากมีปริมาณเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติในกลุ่มส่วนของต่อมลูกหมากที่เพิ่มขึ้นกับค่า PSA ที่สูงขึ้นข้างใน ในการตรวจ IPSS หลอดเลือดใหญ่ยิ่งมีนัยสำคัญทางสถิติ (p = 0.001)

สรุป: ผู้ป่วยที่ได้รับฮอร์โมนเทสโทสเตอโรน อาการตรวจอัลตราซาวด์และการตรวจต่อมลูกหมากทางทวารหนัก นั้นต่อมลูกหมากส่วน central gland ในช่วง 6 เดือนหลังการรักษา และพบว่ามีความสัมพันธ์กับการเพิ่มขึ้นของต่อมลูกหมากมากกว่าส่วนอื่น ๆ ที่เพิ่มขึ้นกับค่า PSA ที่สูงขึ้นข้างใน ในการตรวจ IPSS หลอดเลือดที่ใหญ่ยิ่งมีนัยสำคัญทางสถิติ (p < 0.001)