Simultaneous Measurements of Follicle Stimulating Hormone and Total Testosterone and Associations in Clinically Localized Prostate Cancer

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**Key Words**
Prostate cancer • Endocrine axis • Serum testosterone • Follicle stimulating hormone • Tumor grade • Tumor volume

**Abstract**

**Objectives:** To evaluate the potential relations of simultaneous measurements of basal levels of follicle stimulating hormone (FSH) and total testosterone (TT) in clinically localized prostate cancer (PCa).

**Materials and Methods:** The study included 126 patients who had simultaneous measurements of prostate specific antigen (PSA), FSH, and TT before undergoing radical prostatectomy for clinically localized PCa. Correlations and independent associations between clinical and pathological factors were investigated by statistical methods.

**Results:** The tumor volume (TV) was directly correlated to PSA and TT which was inversely related to FSH. Moreover, it was independently associated with both PSA and TT. In a multivariate linear regression model, FSH and TV were simultaneous independent factors associated with TT. The association was inverse in the former and direct in the latter. In the patient population, the subset with FSH levels above the third quartile was related to lower median levels of TT that were associated with high grade cancer showing a lower TV. In localized PCa, basal levels of TT were associated with tumor parameters and inversely related to FSH levels, and the subset FSH levels above the third quartile were related to lower TT levels that were associated with high grade cancers showing a lower tumor load. **Conclusion:** Preoperative TT was associated with tumor parameters and inversely related to FSH levels. Patient with increased FSH levels was related to lower levels of TT, which was associated with high grade cancer.

**Introduction**

The gonadotroph cells of the anterior pituitary gland produce the follicle stimulating hormone (FSH) and luteinizing hormone (LH) which stimulate the gonads. The interstitial cells of Leydig are responsible for the production of 95% of all circulating androgens in the form of testosterone. Approximately 98% of the circulating androgens are bound to plasma proteins, including a specific beta-globulin, testosterone-estradiol binding...
globulin. The free testosterone (FT) in the blood is the physiologically important fraction. Androgens and estrogens regulate prostate growth.

It has been shown that prostate cancer (PCa) is androgen dependent [1], relates to total prostate specific antigen (PSA) levels [2–4], and is associated with abnormal total testosterone (TT) and FT basal levels [5–12].

Receptors of both FSH and LH have been detected in benign prostatic hyperplasia and PCa tissues [13–17]. These findings suggest that FSH and LH may induce and indirectly promote cancerogenesis of the prostate by stimulating the production of TT or directly by triggering their receptors [18]. The pathophysiology of PCa remains almost unknown [19]. Studies exploring the hypothalamic-pituitary-testis-prostate axis have shown that the tumor may produce a substance that alters the levels of LH and FSH [5, 9–12, 20–27]. Although it has been suggested that high grade PCa negatively impacts along the endocrine axis [25], this hypothesis has not been confirmed [28].

In PCa patients, it has been shown that high basal serum levels of FSH are detected in 23% of cases and are associated with abnormal FT and PSA levels [29, 30]. In surgical specimens, it has also been demonstrated that basal levels of TT are associated with high risk PCa [31, 32] and tumor upgrading [33]. The aim of the present investigation was to evaluate the potential relations of simultaneous measurements of basal levels of FSH and TT in clinically localized PCa.

Materials and Methods

The present analysis was part of a study aimed at evaluating a potential link between PCa and the hypothalamus-pituitary-testis-prostate axis. Collection and use of data for analysis had Institutional Review Board approval. The study included 240 patients who underwent radical prostatectomy with or without limited lymph node dissection in a period from December 2007 to December 2011. Exclusion criteria were as follows: (i) treatment with 5a-reductase inhibitors, LH-releasing hormone analogues, or testosterone replacement or (ii) previous radiation of the pelvis. Patients were classified according to the primary tumor stage, lymph nodes and metastatic status, using the TNM categories recommended by the 1997 International Union Against Cancer TNM classification system [35]. Tumors were graded according to the Gleason grading score system after computing the pathology Gleason pattern (pGP). The overall percentage of cancer volume (V+) was related to the volume of the removed prostate (ml) which was computed as the quotient prostate weight (gram)/prostate tissue specific weight =1.05. The tumor volume (TV; ml) was calculated by multiplying the prostate volume with V+.

Statistical Methods

Data on continuous variables are presented as means with their respective standard deviations. Data on categorical variables are presented as percentages. The association of TV with clinical factors was assessed by correlation analysis after calculating the Pearson’s correlation coefficient (r). The independent association of significant clinical factors with TV was computed by multiple linear regression analysis. The independent association of TT with clinical and pathological factors was investigated by multiple linear regression analysis. All tests are two-sided with p < 0.05 considered to indicate statistical significance.

Results

The summary statistics of clinical and pathological factors assessed in the PCa population (n = 126) are reported in table 1. Table 2 shows the linear correlations of clinical factors associated with TV. As shown, there was a significant correlation of TV with TT (r = 0.243, p = 0.006), PSA (r = 0.441, p < 0.0001), and P+ (r = 0.383, p < 0.0001). Age and prostate volume did not show any association with TV. There was also a negative correlation between TT and FSH (r = -0.213, p = 0.017). The association of clinical factors predicting TV by multiple linear regression models is reported in table 3. The final model showed that TT (p = 0.001), PSA (p < 0.0001), P+ (p < 0.0001), and bGS > 7 (p = 0.009) were independent factors associated with TV.

Table 4 shows linear regression models predicting TT by clinical and pathological factors. The regression coefficients (b) are also reported. The final model showed
that FSH (b = -0.1, p = 0.017), TV (b = 0.2, p = 0.001), and pGP = 4 + 3 (b = -5.3, p = 0.002) were independent factors associated with TT serum levels. Table 5 displays further multiple linear regression models of clinical and pathological factors associated with TT. In these models, TV is transformed into a categorical variable by quartiles as follows: (i) first quartile (TVq1 ≤ 5.3), (ii) second quartile (TVq2: > 5.3, ≤ 7.8), (iii) third quartile (TVq3: > 6.8, ≤ 13.0) and (iv) above the third quartile (TVq4, > 13.0). The final model showed that FSH (b = -0.2, p = 0.010), TV > q3 (b = 3.7, p = 0.006) and pGP = 4 + 3 (b = -5.3, p = 0.003) were independent factors associated with TT basal levels.

Figure 1 depicts the linear negative association between FSH and TT stratified by the absence or presence of pGP = 4 + 3. The regression lines have negative slopes and do not interact. The presence of pGP = 4 + 3 lowers the mean values of FSH and TT along the regression lines. Figure 2 shows the functional relations between FSH and TT after stratifying the population by the presence or absence of pGP = 4 + 3 and TV > q3 according to the final model in Table 5. In the absence of pGP = 4 + 3, the mean levels of FSH and TT detected were higher in

### Table 1. Summary statistics of clinical and pathological factors of the PCa population at diagnosis (n = 126)

| Variables | n (%) | Mean ± SD |
|-----------|-------|-----------|
| Age, years | 65.2 ± 6.5 |
| TT, nmol/L | 16.3 ± 6.5 |
| FSH, IU/L | 8.1 ± 8.1 |
| PSA, ug/l | 7.7 ± 5.5 |
| P+, prop | 0.34 ± 0.20 |
| PV, ml | 58.4 ± 29.6 |
| TV, ml | 10.5 ± 8.1 |

| bGP 3 + 3 | 72 (57.1%) |
| 3 + 4 | 39 (31%) |
| 4 + 3 | 3 (6.3%) |
| > 4 + 3 | 7 (5.6%) |
| cT 1c | 70 (55.6%) |
| 2a | 36 (28.6%) |
| 2b | 18 (14.3%) |
| 3a | 2 (1.6%) |
| pGP 3 + 3 | 38 (30.2%) |
| 3 + 4 | 57 (45.2%) |
| 4 + 3 | 15 (11.9%) |
| > 4 + 3 | 16 (12.7%) |
| pT 2a | 11 (8.7%) |
| 2b | 54 (42.9%) |
| 3a | 51 (40.5%) |
| 3b | 10 (7.9%) |
| pN 0 | 102 (81.0%) |
| 1 | 22 (17.5%) |
| 2 | 2 (1.6%) |

PV = Prostate volume; cT = tumor; TNM clinical staging of prostate cancer; pT = pathologic tumor staging of prostate cancer; pN = pathologic; TNM nodal staging of prostate cancer.

### Table 2. Correlation analysis of clinical factors with tumour volume in the prostate cancer population at diagnosis (n=126)

| Variables | TT | FSH | PSA | PV | P+ | TV |
|-----------|----|-----|-----|----|----|----|
| Age       | r  | 0.000 | 0.182 | -0.130 | 0.198 | -0.031 | 0.490 |
|           | p  | 0.997 | 0.042 | 0.734 | 0.026 | 0.734 |
| TT        | r  | 0.212 | 0.150 | 0.369 | 0.323 |
|           | p  | 0.017 | 0.751 | 0.963 | 0.006 |
| FSH       | r  | -0.112 | 0.081 | -0.089 |
|           | p  | 0.212 | 0.150 | 0.369 | 0.323 |
| PSA       | r  | 0.124 | 0.179 | 0.441 |
|           | p  | 0.167 | 0.045 | < 0.0001 |
| PV        | r  | -0.271 | 0.027 |
|           | p  | 0.002 | 0.766 |
| P+        | r  | 0.383 |
|           | p  | < 0.0001 |

PV = Prostate volume.

### Table 3. Multiple linear regression analysis of clinical factors associating with tumour volume in the prostate cancer population at diagnosis (n = 126)

| Variables | b   | se  | 95% CI of b | p     |
|-----------|-----|-----|-------------|-------|
| Basic model |     |     |             |       |
| TT        | 0.3 | 0.1 | 0.1         | < 0.0001 |
| PSA       | 0.5 | 0.1 | 0.2         | < 0.0001 |
| P+        | 8.8 | 3.2 | 2.4         | 0.007 |
| *bGP 3 + 4 and 4 + 3 | 1.9 | 1.3 | -0.7       | 4.5   | 0.152 |
| *bGP > 4 + 3 | 8.2 | 2.7 | 2.7       | 13.7  | 0.004 |
| Final model |     |     |             |       |
| TT        | 0.3 | 0.1 | 0.1         | < 0.0001 |
| PSA       | 0.5 | 0.1 | 0.2         | < 0.0001 |
| P+        | 10.7 | 2.9 | 4.8        | 16.6  | < 0.0001 |
| *bGP > 4 + 3 | 7.2 | 1.8 | 1.8       | 12.5  | 0.009 |

b = Regression coefficient; se = standard error; CI = confidence interval of the regression coefficient; *reference bGP 3 + 3; **reference bGP ≤ 7; *after removing non significant factors; TV is the dependent variable.
patients with TV > q3. The regression lines having both
negative slopes and showing interaction when FSH levels
are between 30 and 40 IU/l. The slope of the regression
line of FSH predicting TT remains negative in patients
with pGP = 4 + 3 and TV < q3 while it shows a positive
orientation in cases with pGP = 4 + 3 and TV > q3. The
regression lines interact at FSH levels between 10
and 15 IU/l. Figure 3 depicts the relationships between mean

Table 4. Multiple linear regression analysis of factors associating with TT
in the PCa population at diagnosis (n = 126)

| Variables     | b    | SE   | 95% CI of b Lower | 95% CI of b Upper | p    |
|---------------|------|------|-------------------|-------------------|------|
| Basic model   |      |      |                   |                   |      |
| FSH           | -0.2 | 0.1  | -0.286            | -0.01             | 0.011|
| TV            | 0.2  | 0.1  | 0.057             | 0.3               | 0.006|
| pGP = 3 + 4   | 1.2  | 1.2  | -1.3              | 3.7               | 0.359|
| pGP = 4 + 3   | -4.1 | 1.9  | -7.9              | -0.4              | 0.030|
| pGP > 4 + 3   | 2.5  | 1.8  | -1.2              | 6.2               | 0.183|
| Final model   |      |      |                   |                   |      |
| FSH           | -0.1 | 0.1  | -0.3              | -0.03             | 0.017|
| TV            | 0.2  | 0.1  | 0.4               |                   | 0.001|
| pGP = 4 + 3   | -5.3 | 1.7  | -8.6              | -1.9              | 0.002|

b = Regression coefficient; SE = standard error; CI = confidence interval
of the regression coefficient; *reference pGP = 3 + 3; references pGP = 3 + 3 and > 4 + 3; after removing non-significant factors.

Table 5. Multiple linear regression models of factors associating with TT
in the PCa population at diagnosis (n = 126)

| Variables     | b    | SE   | 95% CI of b Lower | 95% CI of b Upper |
|---------------|------|------|-------------------|-------------------|
| Basic model   |      |      |                   |                   |
| FSH           | -0.2 | 0.1  | -0.286            | -0.01             |
| TV (q2)      | 1.1  | 1.6  | -2.0              | 4.3               |
| TV (q3)      | 1.2  | 1.5  | -1.7              | 4.2               |
| TV (> q3)    | 4.5  | 1.6  | 1.3               | 7.6               |
| Final model   |      |      |                   |                   |
| FSH           | -0.2 | 0.1  | -0.3              | -0.04             |
| TV (q2)      | 3.7  | 1.3  | 1.1               | 6.2               |
| TV (> q3)    | -5.3 | 1.7  | -8.7              | -1.9              |

b = Regression coefficient; SE = standard error; CI = confidence interval
of the regression coefficient; *reference TV (q1) at the first quartile; TV (q2), TV between the first and second quartile; TV (> q3), TV upper to the third quartile; *reference TV lower than the fourth quartile; *references pGP = 3 + 3; *references pGP = 3 + 3 and > 4 + 3; after removing non-significant factors.

Fig. 1. The linear negative association between FSH and TT stratified by pGP = 4 + 3. The regression lines have negative slopes and do not interact. The presence of pGP = 4 + 3 lowers the mean values of FSH and TT along the regression lines.

Fig. 2. The functional relations between FSH and TT after stratifying the population by pGP = 4 + 3 and TV according to the final model reported in Table 5.

FSH and Total Testosterone in Localized Prostate Cancer
levels of TT at the different pGP points when patients are stratified by TV > q3. As shown, the lowest mean levels of TT were detected at pGP = 4 + 3 in both groups. However, the mean levels of TT detected were higher in cases with TV > q3 at the other points of pGP (3 + 3, 3 + 4, 4 + 4, > 4 + 4). Figure 4 shows the functional rela-
tionships of mean levels of FSH at the different points of pGP. As shown, the highest levels of FSH were at pGP = 4 + 4 and TV < q3. However, the lowest mean levels of FSH were detected at pGP > 4 + 4. Figure 5 shows the mean levels of PSA at the different points of pGP when patients were stratified by TV > q3. The mean levels of PSA detected were higher at the different pGP points in patients with TV > q3. However, high grade tumors also showed low mean levels of PSA in cases with TV < q3. As shown, a high rate of cases with TV > q3 was detected at pGP = 4 + 3.

As shown in table 2 and 3, independent positive associations were detected between TV and preoperative clinical factors including TT, PSA, P+, and bGS > 7. However, as shown in table 2, 4, and 5, basal TT levels, although directly associated with aggressive tumor biology, were inversely related to FSH serum measurements. The associations of basal TT levels with tumor biology (volume and grade) and with the pituitary-testis-prostate axis are shown in figure 1 to 6.

Discussion

In our study, we found significant basal functional relationships between PCa and the pituitary-testis-prostate axis. In the surgical specimens, independent positive associations were detected between tumor parameters (volume and grade) and preoperative clinical factors along the testis-prostate-axis. Interestingly, the investigation showed that PSA and TT were specific factors targeting tumor biology. The deep meaning of the relationships between PCa and TT as well as between PCa and PSA are well explained by the reported diagrams. At diagnosis of PCa, large tumors might be detected along all the different pGP points in the surgical specimens (fig. 6). At each of these points, different mean basal levels of TT and PSA were detected when we stratified the tumors by their volume (fig. 3, 5). As a result, large high grade tumors (pGP = 4 + 4) were associated with high mean levels of TT and PSA as well as small high grade tumors related to low mean basal levels of TT and PSA. Moreover, large low grade tumors (pGP = 3 + 3) were associated with higher mean TT levels than the small ones. Interestingly, in the multivariate model, pGP = 4 + 3 had a negative regression coefficient (table 4, 5) indicating a negative association with TT. Intermediate grade cancers (pGP = 4 + 3) had the lowest TT levels and did not show any difference between large and small volumes. This finding triggers the basic research hypothesis which needs further assessment. Large high grade tumors (pGP = 4 + 4) have been associated with higher mean levels of TT and PSA as well as small high grade tumors related to low mean levels of TT and PSA. The same has been true for low grade cancers (pGP = 3 + 3). Our study gives evidence that PCa tumors are not homogenous at diagnosis and different phenotypes may be detected. As a consequence, the high grade phenotypes with a high tumor load associate with high TT and PSA levels as well as those with low tumor load relate to low TT and PSA levels. The same is true for the low grade cancers. As a consequence, along the testis-prostate axis, TT and PSA are significant clinical factors targeting tumor biology.

The results of our study are interesting for interpreting and understanding the actual confusion and controversy related to the critical topic dealing with the association of basal TT levels and biology of PCa [36, 37].

Our investigation also showed significant associations between the pituitary-testis-prostate axis and tumor biology. Basal TT levels, while associated with aggressive tumor biology, are inversely related to FSH serum measurements. The associations of basal TT levels with tumor biology (volume and grade) and with the pituitary axis (FSH levels) are shown in figures 1 to 4. Interestingly, we found important associations between FSH and TT serum levels (findings not shown in the results section). FSH quartile levels were as follows: (i) first quartile: within 3.8 IU/l, (ii) second quartile: above 3.8 IU/l and within 6.3 IU/l, (iii) third quartile: above 6.3 but within 9.1 IU/l, and (iii) fourth quartile: above 9.1 IU/l. The population was divided into above the third quartile versus within the third quartile. Interestingly, TT median levels were significantly lower (12.2 ng/ml) in the former (p < 0.0001) when compared to the latter (16.3 ng/ml). As a result, FSH serum levels above the third quartile (25% of cases) targeted a subgroup having lower median levels of TT. Interestingly, from figure 3 and 4 it can be seen that high grade tumors (pGP = 4 + 4) with lower cancer load show higher basal median levels of FSH but lower median levels of TT when compared to high volume cancers showing the opposite. As a result, the endocrine axis targets a class of high grade tumors (pGP = 4 + 4) in which the volume of the tumor associates with different levels of FSH and TT. Our study presents interesting findings on FSH pathophysiology in PCa patients and supports literature findings dealing with this controversial subject. Because of the associations between basal FSH levels and tumors, FSH might be a complementary
tool for assessing PCa biology. It has been shown that significant higher FSH levels are associated with locally advanced PCa after retropubic radical prostatectomy in patients with clinically localized disease [38]. Moreover, in patients undergoing androgen deprivation therapy for advanced PCa, elevated FSH basal levels are associated with early development of castration resistant PCa [39]. The associations between basal FSH levels and PCa indicate the complex heterogeneity of PCa biology. Basic research has shown that FSH is produced by PCa tumors which also express FSH receptors. As a consequence, FSH might have an effective potential role along the different steps of PCa cancerogenesis [40, 41]. Moreover, the FSH receptor might be effective for therapeutic purposes [40–42].

There are limits in our study. First, the data were retrospectively evaluated. Second, PSA density was not measured because the volume of the prostate was not measured at biopsy. Third, intraprostatic measurements of TT and FSH were not performed. Fourth, FSH receptors of the tumor were not investigated. However, beyond the limits of the study, we are confident that our investigation presents interesting findings relating basal FSH, TT, and PSA levels to tumor biology.

Conclusion

In the surgical specimens of patients with localized PCa, basal levels of TT were associated with tumor parameters and inversely related to FSH levels along the endocrine axis. In the patient population, the subset with increased levels of FSH above the third quartile was related to lower levels of TT that associated with high grade cancers showing a lower tumor load. In the future, basal levels of both TT and FSH might express the potential of targeting functional relationships between the endocrine axis and PCa.

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FSH and Total Testosterone in Localized Prostate Cancer

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