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Low testosterone levels are related to poor prognosis factors in men with prostate cancer prior to treatment

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Abstract

Study Type – Prognosis (case series)

Level of Evidence 4

What's known on the subject? and What does the study add?

Prostate growth is ruled by testosterone. Nevertheless, the paradigm that high testosterone levels induce prostate cancer development or lead to a poor prognosis in prostate cancer is not supported by evidence. A growing number of studies suggest that, on the contrary, low testosterone levels are related to poor prognosis features in prostate cancer such as higher prostate-specific antigen or higher Gleason score.

Our experience shows that testosterone levels are related to risk of progression of prostate cancer – those men with lower testosterone levels are at higher risk of progression of their prostate cancer after treatment delivery.

OBJECTIVES

- Low testosterone levels have been related to a higher diagnosis of prostate cancer (PCa). Hormonal levels have been related to poor prognosis factors in men with PCa, mainly after radical prostatectomy.
- Our aim was to determine the relationship between hormonal levels and PCa prognosis factors in men with PCa prior to the onset of treatment.

PATIENTS AND METHODS

state biopsies from February 2007 to December 2009.

• As part of our clinical protocol, we performed hormonal determination (testosterone and sex hormone binding globulin) following International Society of Andrology, International Society for the Study of the Aging Male and European Association of Urology recommendations.

• Free testosterone and bioavailable testosterone were calculated using Vermeulen's formula.

• Age, prostate-specific antigen (PSA), free to total PSA, PSA density, number of previous biopsies, digital rectal examination staging, Gleason score, percentage of tumour in the biopsy sample, bilaterality of the tumour and risk of progression group were prospectively recorded.

RESULTS

• Higher testosterone levels were related to lower digital rectal examination staging (P= 0.02) and lower PSA level (P= 0.05). Higher testosterone was not related to lower Gleason score (P= 0.08).

• Testosterone was inversely related to PCa bilaterality ($P < 0.01$) and percentage of tumour in the biopsy ($P < 0.01$).

• High testosterone levels were found in patients allocated to the low risk of progression group and inversely (P= 0.03).

• In multivariate analysis, higher age and lower testosterone were related to higher D'Amico risk of progression.

CONCLUSION

• Patients with PCa and lower testosterone levels have poor prognosis factors and higher tumour burden before treatment onset. These findings reinforce the idea that low testosterone levels pretreatment are related to a poor prognosis in PCa.

Abbreviations

PCa
prostate cancer
RP
radical prostatectomy

INTRODUCTION

The relationship between testosterone and prostate cancer (PCa) is controversial and the evidence is conflicting. Since Huggins *et al*. [1,2] published their studies on the response of PCa to testosterone deprivation in the early 1940s, testosterone has been considered as ‘fuel to the fire’ of PCa.

How as prostate cancer detection increases [3]. Up to now, no study has related high testosterone with increased risk of PCa development. On the contrary, some data show that PCa might be found at lower bioavailable testosterone levels [4–6]. Moreover, there is evidence that low serum testosterone levels may be related to worse prognosis and aggressiveness factors in PCa patients after radical prostatectomy (RP) [7–14].

Most of the available data about PCa and testosterone arise from studies of patients who have undergone RP. There are few data about the hormonal pattern and factors affecting PCa diagnosis and prognosis at prostate needle biopsies [15–18] before treatment was applied. After the diagnosis of PCa has been obtained, D'Amico risk of progression classification and others are of help in predicting PCa prognosis using clinical data and information from the TRUS prostatic biopsy, before treatment is delivered and final pathological data are available.

Our aim was to analyse the hormonal pattern and its correlation with broadly established PCa prognosis factors pretreatment (such as PSA, DRE and Gleason score, and specifically D'Amico risk of progression) in order to determine the value of the hormonal pattern as an indicator of subsequent PCa outcome.

PATIENTS AND METHODS

We prospectively analysed 137 males with PCa diagnosed in our centre after TRUS prostate biopsy from February 2007 to December 2009. The indication for prostate biopsy was suspicious DRE or PSA elevation. Diagnosis was carried out with 5+5 core TRUS-guided prostate biopsy. As part of our clinical protocol, we determined the hormonal pattern (testosterone and sex hormone binding globulin [SHBG]) in these patients.

Serum samples were obtained by venipuncture of fasting patients between 7:00 and 11:00 am. Testosterone and SHBG (automated immunometric chemoluminescent method, Cobas Roche) were determined. Free testosterone and bioavailable testosterone were calculated using Vermeulen's formula. Men with testosterone <346 ng/dL were considered to have low testosterone levels.

We prospectively recorded age, number of previous biopsies, PSA, free-to-total PSA (fPSA), PSA density (dPSA), DRE, prostate volume and pathological data (Gleason score, percentage of biopsy affected by tumour, bilaterality of the tumour). To describe the tumour burden, in our centre the amount of tumour in the biopsy is given as a percentage ranging from >0% to 100% in each prostatic lobe (percentage of tissue from the total amount of tissue of the biopsy; i.e. men with 5% tumour in the left prostatic lobe and 40% tumour in the right prostatic lobe would have a total of 45% tumour in the biopsy sample).

Age and prostate volume were analysed as continuous variables. PSA and its surrogates (dPSA, fPSA) were analysed as continuous variables and the PSA as a categorical variable (PSA < 10, PSA 10–20 and PSA > 20). DRE was analysed as a categorical variable (T1, normal DRE; T2, suspicious of organ confined prostate cancer; ≥T3, suspicious of non-organ confined prostate cancer).

Specifically we analysed the D'Amico risk of progression classification as a reliable and widely spread pretreatment classification of risk of PCa progression. Tumours were subclassified depending on their risk of

prog)RE = T2b and Gleason score 7; high risk, PSA > 20 or DRE ≥ T2c or Gleason score ≥8 [19].

A multivariate analysis between hormonal pattern (specifically testosterone and SHBG) and age was performed to define which variables were related to D'Amico risk of progression.

SPSS software (SPSS Inc., Chicago, IL, USA) was used to analyse the study data. $P < 0.5$ was considered statistically significant.

RESULTS

Clinical, pathological, biochemical and hormonal data of the 137 patients enrolled in the study are shown in Table 1. The results of the analysis between independent variables and the hormonal pattern are displayed in Table 2.

Table 1. Main clinical, biochemical, pathological and hormonal data of the 137 men included in the study

Age (years) (mean ±SD)	**68.8 ± 9**
PSA (ng/mL) (mean ±SD)	65 ± 497
PSA < 10	87/137 (65.9%)
PSA 10–20	30/137 (22.7%)
PSA > 20	15/137 (11.4%)
DRE	
T1	87/137 (63.5%)
T2	45/137 (32.8%)
≥T3	5/137 (3.6%)
Number of biopsy	
First biopsy	95/122 (77.9%)
Second biopsy	13/122 (10.7%)
Third or further biopsy	14/122 (11.4%)
Gleason score	
Gleason 2–6	80/137 (58.4%)
Gleason 7	40/137 (29.2%)

D'Amico risk of progression groups: low risk, PSA < 10, DRE ≤ T2a and Gleason score ≤6; intermediate risk, PSA 10–20, DRE = T2b and Gleason score 7; high risk, PSA > 20 or DRE ≥ T2c or Gleason score ≥8.

Table 2. Result of the univariate analysis between clinical, pathological and biochemical variables and hormonal variables and their P values

	Testosterone (ng/dL)	***P***	**SHBG (nmol/L)**	***P***	**Free testosterone (ng/dL)**
PSA		0.05		0.108	
<10	464 ± 162		48 ± 18		7.9 ± 3.1
10–20	418 ± 159		61 ± 45		6.1 ± 2.1
>20	350 ± 174		53 ± 13		5.3 ± 2.6
DRE		0.02		0.622	
<T2b	451 ± 164		52 ± 27		7.4 ± 2.7
T2b	408 ± 194		57 ± 82		6.1 ± 3
>T2b	305 ± 152		46 ± 19		5 ± 2.2
Gleason		0.08		0.436	
2–6	452 ± 180		54 ± 30		7.2 ± 2.5
7	441 ± 159		49 ± 27		7.4 ± 3.4
8–10	347 ± 115		46 ± 10		5.8 ± 2.4
D'Amico risk of		0.03		0.441	

D'Amico risk of progression groups: low risk, PSA < 10, DRE ≤ T2a and Gleason score ≤ 6; intermediate risk, PSA 10–20, DRE = T2b and Gleason score 7; high risk, PSA > 20 or DRE ≥ T2c or Gleason score ≥ 8. Bilaterality: presence of tumour in both prostatic lobes. Percentage of positive biopsy: percentage of tissue affected by tumour from the total tissue sample.

The [illegible] is displayed in Fig. 1. Finally, a visual representation of the analysis between testosterone levels and D'Amico risk of progression is shown in Fig. 2.

Lower testosterone levels were related to higher PSA (P= 0.05), higher clinical staging (P= 0.022), poorer D'Amico risk of progression (P= 0.03), higher rate of bilaterality (P= 0.000) and higher tumour burden (P= 0.006). No relationship was found between hormonal pattern and Gleason score when analysed as a three-categories variable, although a certain trend was appreciated (P= 0.08). We analysed hormonal pattern in relationship to Gleason score analysed as a two-categories variable: Gleason ≤ 7 or Gleason > 7. Testosterone was found to be related to Gleason score (testosterone Gleason ≤ 7, 448 ± 173 ng/dL, vs testosterone Gleason > 7, 347 ± 115 ng/dL; P= 0.026).

Low testosterone levels (testosterone <346

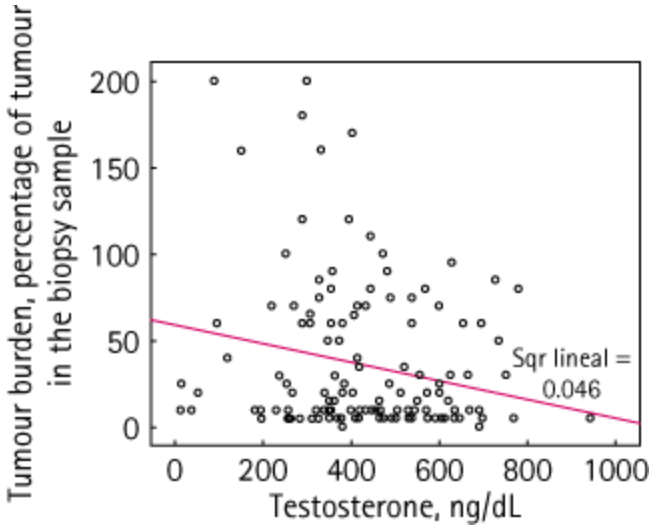

Figure 1 Open in figure viewer PowerPoint

Testosterone levels and percentage of biopsy affected by tumour. Linear regression between the variables testosterone and percentage of tumour representation in the biopsy sample is displayed (P < 0.01). In our centre, the tumour burden in the biopsy is expressed as the percentage of tumour in each prostatic lobe, ranging from >0% to 100%. Thus, the percentage of tumour represented in the biopsy adding the two prostatic lobes ranges from >0% to 200%.

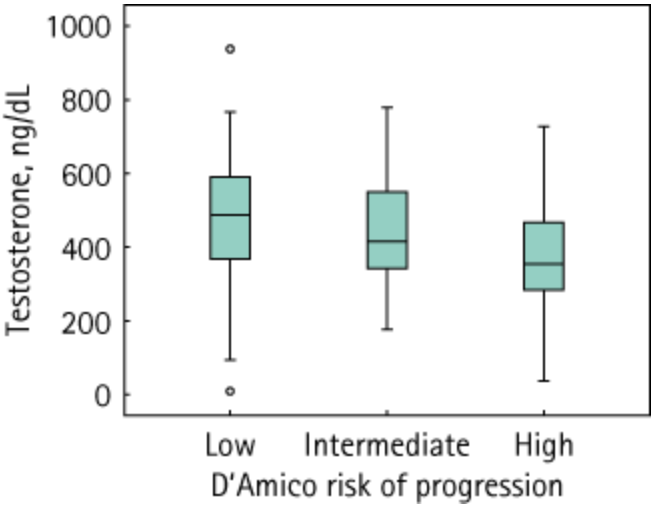

Figure 2 Open in figure viewer PowerPoint

ng/dL, according to their D'Amico risk of progression: low risk, PSA < 10, DRE ≤ T2a and Gleason score ≤6; intermediate risk, PSA 10–20, DRE = T2b and Gleason score 7; high risk, PSA > 20 or DRE ≥ T2c or Gleason score ≥8. Low risk, testosterone 470 ± 171 ng/dL; intermediate risk, testosterone 445 ± 151 ng/dL; high risk, testosterone 365 ± 162 ng/dL; *P*= 0.03.

be related to D'Amico risk of progression (testosterone <346 ng/dL, low risk 38%, intermediate risk 51%, high risk 11%, vs testosterone >346 ng/dL, low risk 29%, intermediate risk 41%, high risk 30%; *P*= 0.043). Moreover, low testosterone was related to tumour bilaterality (25.5% of bilateral tumours in >346 ng/dL vs 50% of bilateral tumours in >346 ng/dL; *P*= 0.009) and tumour burden (32% of tumour in men with testosterone >346 ng/dL vs 53% in <346 ng/dL; *P*= 0.001).

When comparing the statistical analysis between testosterone and free and bioavailable testosterone with clinical end-points, testosterone and bioavailable and free testosterone were found to be significantly related to the same clinical variables (PSA classification, DRE, D'Amico risk of progression and bilaterality) except for percentage of positive biopsy, where testosterone was statistically related (*P*= 0.006) to the burden of tumour but free and bioavailable testosterone were not (*P*= 0.128 and *P*= 0.126).

A multivariate analysis between testosterone and age in relationship to D'Amico risk of progression was carried out. Testosterone (*P*= 0.038) and age (*P*= 0.000) but not SHBG (*P*= 0.816) were related to D'Amico risk of progression. We found no statistical significance between age groups and Gleason score: Gleason < 7, mean age 67 ± 8.7, vs Gleason ≥ 7, mean age 69 ± 9.7; *P*= 0.324.

DISCUSSION

Although prostate growth is regulated by androgens and androgenic deprivation causes PCa to regress [1,20], there is a shift in the paradigm of considering testosterone as a risk factor for prostate cancer [3,21–23]. In this sense the literature shows that high testosterone levels are not related to a higher risk of PCa and, on the contrary, low testosterone levels might be related to more prevalence of PCa [5] and poor PCa prognosis [7–14] .

We analysed a cohort of men diagnosed in our centre with PCa after prostate biopsy due to PSA elevation or abnormal DRE, before a decision on treatment was discussed. In this subset of patients, our study shows that low testosterone levels are related to higher PSA, higher DRE staging and higher tumour burden (represented by tumour bilaterality and higher percentage of tumour representation in the biopsy). When we analysed hormonal pattern in relation to D'Amico risk of progression, lower testosterone levels were related to higher D'Amico stages. Thus, lower testosterone men harbour larger tumours (higher percentage of biopsy affected by tumour, higher rate of bilateral tumours and higher DRE staging), have higher PSA levels and show a certain trend towards higher Gleason scores (specifically Gleason score >7). Thus, men with low testosterone are more likely to have a higher risk of progression after treatment is delivered.

In pr higher Gleason score [10–12], higher pathological stage [7–9], higher rate of PSA > 10 [7], higher rate of positive margins [13] and higher risk of biochemical failure [14] (Table 3).

Table 3. Summary of the studies analysing the relationship between PCa and hormonal pattern

Author	Patients	Findings	Testosterone cut-point
Hoffman *et al.* **[11]**	117 PCa (57 RRP), retrospective	7/64 patients had higher Gleason score in low testosterone patients vs 0/48 in normal testosterone patients Low free testosterone patients had higher stage	300 ng/dL
Schatzl *et al.* **[12]**	156 PCa, prospective	Gleason score 7.2 in low testosterone patients vs 6.4 normal testosterone patients	300 ng/dL
Yamamoto *et al.* **[14]**	272 RPP, retrospective	Low testosterone patients had higher 5-year PSA recurrence rate (OR 2.7)	300 ng/dL
Teloken *et al.* **[13]**	64 RRP, retrospective	Low testosterone patients had higher rate of positive margins (39% vs 14.6%)	270 ng/dL
Lane *et al.* **[10]**	455 RRP, prospective	Low testosterone patients had higher risk of patterns 4–5 (OR 2.4)	220 ng/dL
Isom-Batz *et al.* **[7]**	326 RRP, retrospective	Low testosterone patients had higher stage and had higher rate of PSA > 10	300 ng/dL

Testosterone cut-point used to define hypogonadism. RRP, radical retropubic prostatectomy; OR, odds ratio.

Nevertheless, there are few data about pretreatment testosterone levels and their relationship with clinical pretreatment prognostic factors [16] (Table 3). In our opinion, analysing only RP patients might induce a selection bias, taking into consideration that RP patients are younger and fit compared with those submitted for external beam radiotherapy, cryotherapy or androgen suppression. Thus, our patients include not only young patients in good health with a low tumour stage but also older, unfit and higher stage patients who would probably have lower testosterone levels. In our opinion our population is more representative of patients with PCa than if we had only considered patients undergoing RP.

Our [illegible] levels are related to higher PSA and higher staging, and subsequently higher risk of treatment failure and PSA relapse. A certain trend was observed when analysing low testosterone in relation to higher Gleason scores, a relationship that has already been published. To our knowledge, the link between risks of progression groups, tumour burden in the biopsy sample and hormone levels has not been published to date. We hypothesize that testosterone level is useful as a pretreatment tool to help us define prognosis and risk of progression, and thus help us in better counselling patients.

Low testosterone levels seem to be related to PCa and with worse prognosis factors. On the other hand, castration induces metastatic prostate cancer to regress. The proposed hypothesis for this apparent contradiction [3,21–23] suggests that cancer cells are stimulated to dedifferentiate in a testosterone-deficient environment, leading to more aggressive tumours and a higher Gleason stage. From our point of view and according to our data, our opinion is that both age and hormones play a role in the development of high risk PCa. As hormones are deeply dependent on age, it could be said that aging is relevant and hormones are only incidentally related to PCa. However, we found that the difference in testosterone values for high and low grade tumours was not likely to be due to age, as these do not vary between groups (*P* non-significant).

Some limitations of our study must be taken into consideration. First, ours is a single-centre, rather short series. Thus, selection bias might be present. Although the sample is relatively small, we were able to reach statistical significance in showing the link between PCa prognosis factors and hormonal pattern. Second, our study was cross-sectional and this fact should be noted: PCa and testosterone are evolving entities through years and decades. Thus, our static analysis may be incomplete as no follow-up was considered.

In conclusion, in our study patients with adenocarcinoma of the prostate and lower testosterone levels are affected by more extensive disease (higher clinical staging), higher tumour burden (higher rate of bilateral tumours and higher biopsy affected by tumour) and poorer prognosis (higher PSA, higher D'Amico stages). Pretreatment testosterone determination could contribute to determination of the optimum treatment in men with adenocarcinoma of the prostate.

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CONFLICT OF INTEREST

None declared.

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