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Study of testosterone as a predictor of tumor aggressiveness in patients with prostate cancer

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ABSTRACT

Purpose: A growing body of evidence suggests that low testosterone can be an independent predictor of adverse clinicopathological features and worse prognosis in prostate cancer (PCa) patients. However, this association is still incompletely understood and the results are divisive. The aim of this study was to analyze testosterone as a predictor of aggressive disease in subjects with clinically localized PCa.

Materials and Methods: A cohort was conducted including the patients submitted to radical prostatectomy in our institution during a period of four years. The patients had clinically localized disease and their total testosterone (TT) was routinely measured preoperatively in the morning before surgery. They were stratified in groups with low (< 300 ng/dL) and normal TT (≥ 300 ng/dL). Tumor aggressiveness was inferred based on preoperative PSA levels, pathological Gleason score (lower, equal or greater than 7), TNM stage and surgical margins status.

Results: After analyzing 164 patients we found a significant association between mean preoperative TT and extraprostatic disease (379 for pT3 vs. 421 ng/for pT2 - $p < 0.001$, AUC > 0.99). Conversely, men with high Gleason score had similar mean TT compared to those with lower scores. Preoperative low TT (defined as TT < 300 ng/dL) could not be statistically correlated with either preoperative PSA levels, pathological Gleason score, extraprostatic extension, positive surgical margins or seminal vesicles involvement.

Conclusions: This study indicates that testosterone may be a useful predictive tool once pathological extraprostatic extension was somewhat signaled by lower TT levels preoperatively. However, it does not consolidate a clear association between aggressive tumor biology and hypogonadism.

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INTRODUCTION

Prostate cancer is a biologically heterogeneous disease and both indolent and aggressive tumors are found in clinical practice (1). Defining in which group a patient fits is critical for selecting the adequate treatment. In fact, there has been extensive research in this area and three major prognostic factors were universally established, namely the clinical TNM stage of the disease, preoperative levels of PSA, and degree of tumor differentiation as expressed by the Gleason score (1).

Testosterone is a hormone necessary for the development of the prostate and has been considered for more than 70 years an inductor of proliferation of normal and cancerous cells (2). This concept was introduced by Huggins' landmark study demonstrating that androgen deprivation caused

tumoral regression in men with metastatic (but not localized) prostate cancer (3). Interestingly, when analyzing the failure cases, the author found that those with small testes at the time of castration had a poor prognosis, the first description of a more ominous cancer arising in men with low testosterone. Surprisingly, it was not until recently that preoperative testosterone has been investigated as a new marker to identify aggressive disease among men with non-metastatic cancers (4).

While many controversies and uncertainties regarding the correlation between testosterone and the aggressiveness of non-metastatic PCa persist (5), an increasing body of evidence demonstrates not only an association between low total testosterone (TT) and pathologically advanced disease (6-8), but also with more undifferentiated tumors (9-11) and worse prognosis (12).

In addition, the usefulness of testosterone as a prognostic factor for clinically localized PCa in the Brazilian population has yet to be determined. To our best knowledge, there´s only one previous retrospective Brazilian survey of 64 patients that failed to validate TT as a predictor of either pathological stage or Gleason score (13).

The aim of this study was to evaluate prospectively the association between serum TT and clinicopathological features (preoperative PSA, Gleason score, pathological stage and surgical margins status) in patients submitted to radical retropubic prostatectomy (RRP) for the treatment of clinically localized PCa.

MATERIALS AND METHODS

We analyzed a prospective cohort of 164 patients submitted to open RRP and bilateral obturatory lymphadenectomy for the treatment of clinically organ-confined PCa. None of the patients received any type of neoadjuvant therapy or had previous testosterone replacement therapy. We excluded those on medications that could induce testosterone levels decrease, such as glucocorticoids, loop diuretics, cimetidine, digoxin, neuroleptic drugs, opiates, cannabinoids and others. The surgeries were performed by the team of urologists according to the technique previously described by Walsh (14), at the Department of Urology of the Ipiranga Hospital (Brazil), from April 2005 to May 2009. Nerve-sparing was pursued in all the procedures, except when it was judged to compromise oncological principles, in those cases in which there was an induration palpable in the lateral pelvic fascia after the endopelvic fascia was opened or when the neurovascular bundle seemed to be fixed to the prostate at the time it was being released.

The diagnosis of PCa was done by transrectal ultrasound-directed biopsy of a minimum of 12 fragments. The indications for biopsy were PSA > 4 ng/dL or suspect digital rectal examination.

Total testosterone was determined by a single sample of venous blood using a commercially available radioimmunoassay collected in the morning of the day before surgery. Two groups were devised: one with normal TT (≥ 300 ng/dL) and other with low TT (< 300 ng/dL). This threshold to delineate the low TT group was adopted because it is recommended by the American Society of Clinical Endocrinologists to indicate hypogonadism depending on symptoms and widely used in previous studies on testosterone and PCa (15).

The pathological staging of the surgical specimens was based on the 1997 TNM classification (AJCC/UICC). The surgical specimens were assessed for Gleason score, tumor volume, extracapsular extension, seminal vesicle invasion and lymph node involvement. Organ-confined tumors (pT2) included those tumors without extracapsular extension or seminal vesicles invasion. Locally advanced tumors (pT3-T4) included those with extracapsular extension (pT3a) or seminal vesicle invasion (pT3b). According to the Gleason score, patients were divided into low (Gleason < 7), intermediate (Gleason = 7) and high-grade disease (Gleason ≥ 8).

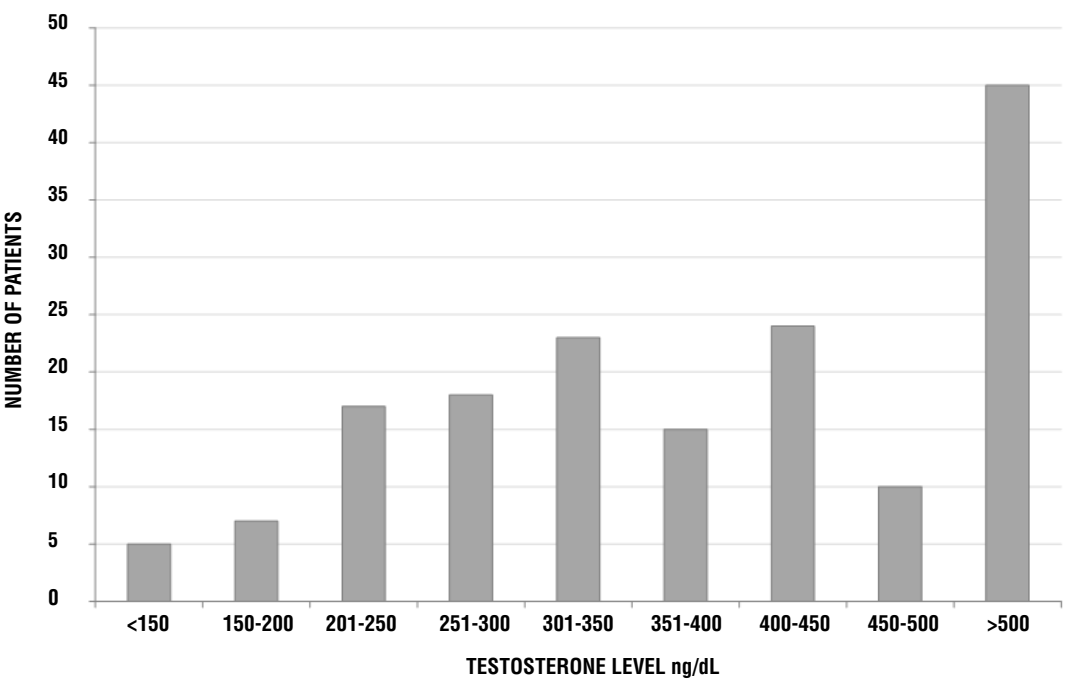
Collected data was allocated in an electronic spreadsheet and statistical analysis was accomplished by a statistician using the Mann-Whitney and Kruskall-Wallis tests for comparing the means of continuous numeric variables, and the likelihood ratio test to analyze proportions of categorized variables (groups with low and normal testosterone). Results were considered significant when $p < 0.05$.

The study was approved by the Ethics Committee of the Institution and informed consent was obtained from all patients before enrollment.

RESULTS

Of the 164 patients included, the mean age, PSA and TT levels were 63.6 years (range: 44-76 years), 9.35 ng/mL and 400.4 ng/dL (range: 92-1050 ng/dL), respectively. Forty-seven patients (28.6%) had low TT. Figure-1 shows the distribution of TT levels in the population.

Figure 1 - Total testosterone levels in the study population.



PSA levels, age or suspicious digital rectal examination did not differ significantly between the groups, but hypogonadal men had higher BMIs (Table-1).

One hundred twenty patients (73.2%) had stage organ-confined disease and 44 (26.8%) were pT3. Mean TT was 421 ng/dL for pT2 and 379 ng/dL for pT3 tumors (Table-2). This difference was statistically significant, with an area under the curve (AUC) > 0.99. In the categorized analysis, the rate of extraprostatic disease was higher in the hypogonadic group: 34% vs. 23.9%, but without statistical significance (Table-3).

Involvement of seminal vesicles was noted in 14 (8.5%) and positive surgical margins in 44 patients (26.8%). The occurrence of these events was comparable in both groups (Table-3). There wasn´t any case of lymph node involvement or T4 tumors.

In regard to tumor differentiation, 70 (42.7%) patients had Gleason < 7, 73 (44.5%) Gleason = 7 and 21 (12.8%) Gleason ≥ 8. The mean levels of TT were statistically equivalent in each one of these groups: 400.6, 432.2 and 365.8 ng/dL, respectively (Table-2). In the categorized analysis,

Table 1 - Baseline clinical characteristics stratified by total serum testosterone.

	Total Testosterone - ng/dL		p value
	< 300	≥ 300	
No. of pts (%)	47 (28.6)	117 (71.4)	Not applicable
Mean age (range)	63.6 (44-76)	62.6 (46-76)	0.50*
BMI - kg/m2 (range)	27.3 (21-34)	25.5 (17-32)	0.006*
Suspicious DRE (%)	17 (36.2)	41 (36)	0.9**
Mean PSA (± SD)	9.25 (7.64)	9.46 (5.57)	0.45*

* Mann-Whitney test. ** Likelihood ratio test
DRE: digital rectal examination.
BMI: body mass index.

Table 2 - Mean total testosterone levels according to the pathological outcomes.

Pathological feature	No. Pts (%)	Mean testosterone level - ng/dL (± SD)	p value
Organ-confined disease (pT2) p(pT2)(p(pT2)	120 (73.2)	421.6 (± 173)	
Extraprostatic disease (pT3)	44 (26.8)	379.1 (± 178)	< 0.001*
Gleason < 7	70 (42.7)	400.6 (± 172)	0.4 **
Gleason = 7	73 (44.5)	432.2 (± 183)	
Gleason ≥ 8	21 (12.8)	365.8 (± 153)	
Total	164 (100)	410.2 (± 175)	

* Mann-Whitney test
** Kruskall-Wallis test.

Gleason scores were also similar in groups with low and normal testosterone (Table-3).

DISCUSSION

The selection of the adequate method of treatment in oncology relies greatly on the balance between the aggressiveness of the disease and the benefits and morbidity of the therapy. This is particularly valid for PCa, a malignancy that is frequently indolent and which treatment (regardless of the method chosen) may be both deleterious and unnecessary. For better patient selection, D´Amico and others have stratified risk

Table 3 - Gleason score and pathological features stratified by total serum testosterone level.

	Total Testosterone - n (%)		p value
	< 300 ng/dL	≥ 300 ng/dL	
No. of pts	47	117	Not applicable
Gleason score			
< 7	23 (48.9)	47 (40.2)	
7	18 (38.3)	55 (47)	0.55
≥ 8	6 (12.8)	15 (12.8)	
Organ-confined disease (pT2)	31 (66)	89 (76.1)	0.19
Extraprostatic disease (pT3)	16 (34)	28 (23.9)	
Seminal vesicles compromised			
Yes	6 (12.8)	12 (10.3)	0.6
No	41 (87.2)	105 (89.7)	
Urethral margin positive			
Yes	10 (24.4)	20 (17.4)	0.3
No	31 (75.6)	95 (82.6)	
Vesical margin positive			
Yes	5 (12.5)	9 (7.9)	0.39
No	35 (87.5)	105 (92.1)	

Likelihood ratio test

groups considering only three major prognostic markers: clinical stage, Gleason score and PSA levels (1). Despite universally accepted these criteria are not flawless and urologists are still limited in their ability to predict pathological tumor stage in a reliable manner (4,5). Understanding other determinants of disease aggressiveness may be extremely helpful in selecting appropriate therapy for individual patients and advances in the comprehension of other prognostic factors such as cancer density in biopsy, third Gleason grade, genetic mutations, tumor characteristics on MRI and, more recently, testosterone have been made (12,16).

Although the data on the association between low testosterone and prognosis of metastatic prostatic cancer is solid (17), the link between serum testosterone and clinically localized PCa

is still incompletely understood and divisive, as we depict in Table-4. While there is evidence that cancers in a low testosterone environment tend to be more aggressive (6-10,12,18,19), many groups failed to demonstrate this association (1,20-22).

Approximately one third of our patients had TT deficiency, accordingly to surveys that also noted an increased incidence of biochemical hypogonadism in PCa patients compared to the general population (15). Again, this scenario is not unequivocal and a recent trial noted a rate of 15% of hypogonadism, which is comparable to the populational prevalence (7).

We adopted as primary endpoints the pathological features (Gleason score, stage, surgical margins status) as determined by the analysis of the surgical specimen because it´s the most reliable manner to determine the actual status of disease and biopsy frequently understages the tumor (16). In our view, this avoids confusing and conflicting results of others who relied exclusively on clinical staging and non-standardized biopsies.

The major finding of this survey was the significant difference in the mean preoperative TT levels when there was non-organ confined disease (421 vs. 379 ng/dL). This association was

Table 4 - Synthesis of the principal studies on the relationship between clinically localized prostate cancer and tumor aggressiveness.

			Clinicopathological features associated with low testosterone				
	No. of cases	Design	Gleason	TNM stage	PSA	Surgical margins	Recurrence
Hoffman (11) (2000)	57	Retrospective	Yes***	No	No	NA	NA
Schatz (13) (2001)	156	Retrospective	Yes	NA	Yes	NA	NA
Massengill (10) (2003) # *	879	Retrospective	No	Yes	No	No	No
Teloken (16) (2005)	64	Retrospective	No	No	No	Yes	NA
Isom-Batz (12) (2005) #*	326	Retrospective	No	Yes	No	NA	No
Imamoto (30) (2005) *	82	Retrospective	No	Yes	No	NA	Yes
Yamamoto (14) (2007)*	272	Retrospective	No	No	No	No	No
Lane (17) (2008)	455	Prospective	Yes	No	No	No	No
Pierorazio (19) (2010)	781	Retrospective	No	No	NA	NA	Yes
Xylinas (8) (2010)**	107	Retrospective	Yes	Yes	No	No	No
Botto (7) (2011)	431	Prospective	Yes	No	Yes	Yes	NA
Salonia (21) (2011)	673	Prospective	No##	No###	No	No	NA
Isbarn (9) (2009)	---	Review	Uncertain	Uncertain	Uncertain	NA	No

NA - not analyzed; # included patients previously to PSA adoption; ## On multivariate analysis, but higher proportion of gleason 8 in the hypogonadic group; ### Association with seminal vesicles invasion when TT < 100 ng/dL, but not with extracapsular extension; * Testosterone not collected in a systematic manner; ** included patients submitted to laparoscopic procedure; *** Relied on biopsy results.

very strong, with an AUC > 0.99. Curiously, when patients were divided in groups of low and normal TT, the rate of pT3 disease was 11% higher in the hypogonadic group, but still not statistically significant. The reasons for this are unknown to the authors. Possibly, this difference may become significant with an inclusion of a higher number of patients. Another pertinent explanation addresses the TT cut-off level of 300 ng/dL adopted by us and other authors. Clearly, while a threshold of 300 ng/dL may be adequate to hypogonadism diagnosis according to consensus definition of endocrinology and urology societies (15), it may be inappropriate to predict tumor aggressiveness. The relatively high mean TT values we found in the groups (421 and 379 ng/dL) support this idea by themselves. Hoffman also reported a mean TT of 490 and 390 ng/dL when Gleason was < 8 or ≥ 8 respectively (9), levels similar to ours and to Imamoto et al., who also correlated lower mean TT with locally advanced PCa (18).

This ability to predict extraprostatic extension in prostatectomy specimens is important because it´s a proven indicator of aggressive disease, determining greater likelihood of clinical progression, greater risk of a positive surgical margin and poorer long-term cancer control (5). Massengill et al. were the first to demonstrate, in a retrospective cohort, results similar to ours less than ten years ago (6). In that study, there was a higher likelihood of non-organ confined disease (pT3–T4) as TT decreased, but testosterone was collected "at the discretion of the treating physician", potentially imparting a selection bias. The only previous study in a Brazilian population is retrospective and analyzed retrospectively 64 patients after RRP, with the only statistically significant association found between low TT and positive surgical margins, which in our experience was not more frequent in the men with TT < 300 ng/dL (13).

We failed to demonstrate that Gleason score or preoperative PSA levels are influenced by preoperative TT levels, like some groups (12,13,18,23) and in contrast to others (9,10,20). In our opinion, this seems somewhat logical because dihydrotestosterone (the most biologically active prostatic androgen) concentration in prostate cells does not reflect the concentration of total testosterone (24). Notably, when DHT was inhibited by finasteride or dutasteride in PCPT (25) and REDUCE (26) trials, a higher proportion of high grade tumors was detected.

Some of the most important outcomes in oncologic treatment are disease recurrence and actual clinical progression. Their relationship with testosterone lacks confirmation (20). Interestingly, there are studies demonstrating a correlation with Gleason score (20) and pathological staging (6,10) but not with PSA recurrence or clinical progression (18,20). In 2007, Yamamoto et al. demonstrated that preoperative TT was an independent predictor of biochemical recurrence, but paradoxically it did not correlate with any pathologic features (Gleason score, pathologic stage, surgical margins). The authors state that the reason of these discrepancies is unclear (12). In a well-conducted prospective study, Lane et al. concluded that low pretreatment TT was associated with Gleason pattern 4-5 cancer at prostatectomy, but not with pathological stage or disease progression thereafter (20). They affirm that "at present, routine measurement of TT in men treated by prostatectomy does not appear to be of any clinical value". An argument can be done, however, because this study used TT, which is not the most biologically active form. In this regard, Hoffman et al. showed that free testosterone correlated with mean percent of biopsies demonstrated cancer (47% vs. 28%, p = 0.018) and also with pathological stage while TT did not (9).

To further confound the scenario, Miller, Zangh and others have demonstrated a normalization of serum testosterone following RRP, raising the question if low TT may be a consequence and not the cause of more aggressive prostate cancer (27-29). They propose the lower TT in patients with more advanced pathological stage may be due to inhibition of the hypothalamic-pituitary by the neoplasia itself (13-15). Another theory is that there is a disruption in the normal growth and maintainance of the prostatic caused by a low testosterone hormonal milieu, leading to compensatory hyperplasia that might result in cell mutations and consequent selection of androgen independent, aggressive prostate cells (10). Actually, the exacts mechanisms of interaction between testosterone and PCa remain unknown.

The greater strength of our study was its prospective design, allowing routine morning testosterone measurement before surgery during a 4 years period and the formation of a cohort of men representative of the reality in which PCa is treated in Brazil, including both high and low-risk disease. To our knowledge, this is also the first prospective study to address testosterone as a predictor of aggressive disease in Brazilian men with clinically localized PCa. Validation of a prognostic factor in a different population is important because prostate cancer may be genetically and clinically diverse in different populations (30).

The limitations of our study include the absence of central pathological review and unavailability of data on long-term post-operative follow-up and survival. Body mass index was lower in the hypogonadic group (a finding shared by others (7)) and we did not control the groups for ethnicity because it´s particularly complex to discriminate race in the Brazilian population, that´s multiracial and heterogeneous. Free and bioavailable testosterone (considered more biologically active forms) were not determined. Furthermore, a single dosage of TT in the day before surgery could imply on an incorrect value, once the stress of preoperative period could modify testosterone levels on an individual fashion (15).

CONCLUSIONS

Preoperative TT was associated with extraprostatic disease and may become a useful tool to improve our ability to recognize more advanced carcinomas. This correlation was not validated for other variables indicative of tumor aggressiveness and is not unequivocally consolidated in the literature. Nonetheless, the concept that testosterone and other androgens have a permissive role and promote the development of PCa seems to be incorrect and an oversimplification in view of the current evidences in the field.

ABBREVIATIONS

BMI: Body mass index
DRE: Digital rectal examination
NA: Not analyzed
PCa: Prostate cancer
PSA: Prostate Specific Antigen
TT: Total testosterone

CONFLICT OF INTEREST

None declared.

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