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Association between low serum free testosterone and adverse prognostic factors in men diagnosed with prostate cancer in KwaZulu-Natal

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Summary

Background. The association of serum free testosterone (FT) with prostate cancer is not fully understood. Studies on the results of the relationship between serum testosterone level and prostate cancer are conflicting. However, there is a reported association between lower serum testosterone levels and high-grade prostate cancer.

Objective. To investigate the relationship between serum FT and the clinico-pathological characteristics of prostate cancer in South African patients.

Materials and methods. The clinical data of 109 consecutive patients diagnosed with prostate cancer on biopsy were evaluated prospectively. The variables were age, ethnic group, prostate-specific antigen (PSA), digital rectal examination (DRE) findings, clinical tumour, nodes and metastases (TNM) stage, and Gleason score. Low serum FT was defined as <250 ng/dl. Statistical analysis was performed using Stata V10 software ($p<0.05$ considered significant).

Results. There was a statistically significant association between low serum FT and high serum PSA, high Gleason score and clinically advanced stage prostate cancer.

Conclusions. In this cohort of men with histologically diagnosed prostate cancer, low serum FT was associated with higher PSA, higher grade, and locally advanced or metastatic prostate cancer.

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The causes of prostate cancer are not well understood, but certain risk factors have been identified, namely age, ethnic group, family history, hormone levels and environmental influences.[1] The role of androgens in the pathogenesis of prostate cancer remains unclear, but is thought to be pivotal. While androgenic stimulation is needed for prostate development and growth, serum testosterone levels have failed to distinguish benign from malignant disease.[2] The responsiveness of prostate cancer to androgen withdrawal and the failure to develop prostate cancer in males castrated before puberty, and in individuals with an inherited 5-alpha-reductase deficiency, support this argument.

However, the serum testosterone level decreases with age (0.25 - 0.40% annually), whereas the incidence of prostate cancer increases.[3] Numerous studies have reported conflicting results concerning the relationship between serum testosterone level and prostate cancer risk.[4,5] Ribeiro *et al.* reported an association between a low serum testosterone level and shorter survival time in men with metastatic prostate cancer,[6] while both Schatzl *et al.* and Zhang *et al.* have shown a correlation between a low serum testosterone level and high-grade prostate cancer.[7,8] Hoffman *et al.* have indicated that patients with prostate cancer and a low free testosterone (FT) level had more extensive disease and a Gleason score of 8 or higher.[9]

In the circulation, testosterone is specifically bound to sex hormone binding globulin (SHBG) (~66%) and nonspecifically to albumin (~33%), leaving only a small fraction unbound (~ 1 - 2%). Unbound free testosterone is considered to be the bioactive fraction able to diffuse across cellular membranes.[10,11]

The objective of this study was to evaluate the relationship between FT levels and various prostate cancer parameters.

Materials and methods

The study included 109 consecutive men with prostate cancer diagnosed in urology clinics at King Edward and St Aiden's Hospitals, Durban, between January 2005 and December 2007. Diagnosis was made via transrectal ultrasound-guided biopsies that were reviewed by a consultant pathologist. The indication for prostate biopsy was a suspicious finding on digital rectal examination (DRE) and/or an elevated serum prostate-specific antigen (PSA) level of 4 ng/dl or more.

Serum samples for hormonal assay were obtained between 08h30 and 12h00. Samples were assayed on the day of procurement. Total testosterone and SHBG were measured by commercially available immunoassays, and FT was calculated (<250 ng/dl in the USA or 23.6 nmol/l in South Africa).[12] Free testosterone was calculated using the free androgen index formula (FAI = TT/SHBG × 100).[13]

Clinical tumour stage was determined by DRE and defined as T1 (prostate feels benign), T2 (palpable nodule confined to one lobe), T3 (tumour extension through prostatic capsule or

into seminal vesicles), and T4 (tumour extension to surrounding structures other than seminal vesicles). Nuclear scintigraphy was used to determine the presence of skeletal metastases (Mx = not known; M0 = skeletal metastases absent; M1 = present).

Statistical analysis

Categorical data were compared using the chi-square test or Fisher's exact test as appropriate. Continuous and ordinal data were compared using the Wilcoxon rank sum test. Data were analysed using Stata V10. A 2-tailed *p*-value <0.05 was accepted as statistically significant.

The study was approved by the local ethics committee. Written informed consent in English or Zulu was obtained from all patients.

Results

The mean patient age was 67.0 years (range 51 - 92 years). The race/ethnicity of the study cohort was black 67.9%, white 15.6%, Indian 8.3% and coloured 8.3%.

Serum FT was normal in 70 patients (64.2%) and low in 39 (35.8%). The mean patient age was 67.1 years in the group with normal FT, and 66.8 years in the group with low FT (p=0.86).

The range of serum PSA in the study cohort was 2.5 - 10 234 ng/ml. The group with low FT compared with the group with normal FT had a significantly greater proportion of patients with serum PSA >20 ng/ml (84.6% v. 61.4%) (see Table 1).

The group with low FT compared with the group with normal FT had: (*i*) a significantly greater proportion with locally advanced (clinical stage T3 - 4) tumours (74.4% v. 48.6%); (*ii*) a significantly greater proportion with metastatic (M1) cancer (48.7% v. 20%); and (*iii*) a significantly greater proportion of patients with a high Gleason score (Table 1).

Discussion

This study is the first prospective analysis of serum FT levels in South African men with prostate cancer. Although the role of androgens in the development of prostate cancer is controversial,[2,3,11] several studies have reported an association between low serum testosterone levels and high-grade or advanced-stage prostate cancer.[2,3,8,9,14] Morgentaler *et al*. showed that the percentage of men with prostate cancer was greater among those with low serum testosterone levels,[15] while Schatzl *et al*. found men with high Gleason scores to have lower serum testosterone and oestradiol levels.[8] In the Massachusetts Male Aging Study, Mohr *et al*. concluded after 8 years of follow-up that testosterone and other androgens (dihydrotestosterone or androstanediol) were not associated with prostate cancer risk.[16] All of these studies dispel the notion that androgens contribute to prostate cancer development.

In the present study, a greater proportion of subjects with low serum FT presented with locally advanced or metastatic prostate cancer compared with the group with normal FT (see Table 1), which supports the finding of Pérez Márquez *et al*., who reported that patients with adenocarcinoma of the prostate and lower testosterone levels are affected by more extensive disease and are at greater risk of progression.[17]

Numerous attempts to correlate serum androgens with serum PSA or prostatic disease have been disappointing and often contradictory. Carter *et al*. analysed the hormone levels of a cohort of patients followed for 15 years before they developed benign prostatic hyperplasia or prostate cancer, and failed to demonstrate any significant association with serum testosterone.[18] Zhang *et al*.[8] hypothesised a possible inhibition of testosterone production by PSA, resulting in a low serum level of the hormone. Our study demonstrated a statistically significant association between low FT and high PSA levels (see Table 1).

Table 1. Association between serum free testosterone and serum PSA, clinical T- and M-stage and Gleason score

	Serum free testosterone				
	Normal (>250 ng/dl)		Low (<250 ng/dl)		
	n	%	*n*	%	*p*-value
Serum PSA					
Low (<10 ng/ml)	13	18.6	2	5.1	
Intermediate (10 - 20 ng/ml)	14	20.0	4	10.3	
High (>20 ng/ml)	43	61.4	33	84.6	0.04
Clinical T-stage					
T1	36	51.4	10	25.6	
T2	31	44.3	18	46.2	
T3	3	4.3	11	28.2	0.001
M-stage					
M0	40	57.1	9	23.1	
M1	14	20.0	19	48.7	0.001
Mx	16	22.9	11	28.2	
Gleason score					
Low	28	40	5	12.8	0.001
Intermediate	26	37.1	16	41	
High	16	22.9	18	46.2	

Massengill *et al.*[19] reported that the pre-treatment testosterone level predicted the pathological (but not clinical) stage in patients with localised prostate cancer. They found no correlation between pathological stage and Gleason score. However, a limitation of their study is that the time of sample procurement was not synchronised to the circadian variation of testosterone release.[19]

Serum FT could theoretically be used to identify a subset of patients with prostate cancer despite a low PSA. In a retrospective study, 14% of patients with a low serum free or total testosterone level who underwent prostate biopsy were found to have prostate cancer, despite a normal DRE or PSA <4 ng/ml.[15] Several studies have shown an association between low serum testosterone levels and higher Gleason score (≥8), higher tumour microvascular density and higher androgen receptor density.[9,20] Similarly, Zang and co-workers found lower testosterone levels in patients with high-grade tumours than in those with moderate-grade tumours or no prostate cancer.[8] This suggests that low testosterone may be an indicator of a poor prognosis in prostate cancer.[20]

Our data support the finding of a relationship between low serum FT and high Gleason score (Table 1). Hoffman *et al.* reported similar results, suggesting that a low serum FT is a marker of more aggressive disease.[9]

Numerous reports in the literature have analysed testosterone changes with ageing. Tenover *et al.* noted decreased 24-hour serum total and FT levels in older subjects.[21] Similarly, Mitchell *et al.* observed a decrease in total testosterone in older patients after grouping them into younger and older populations.[22] In our study, there was no significant relationship between age and FT, probably because this was a selected population of men diagnosed with prostate cancer, rather than a random population sample.

Most South African patients with prostate cancer present with advanced disease, compared with patients in North America and Europe,[23-25] as showed by a recent study by Heyns *et al.*[26] In this study, men with lower than normal FT had a greater proportion with advanced and metastastic disease. Martins and co-workers showed that 38.5% of asymptomatic men with prostate cancer diagnosed in a screening programme in Brazil had T3 - 4 disease;[27] this agrees with our finding, where 57.8% of patients presented with clinical stage T3 - 4 disease. Whether this scenario is attributable to inaccessibility of healthcare, absence of cancer screening, genetics or disease aggressiveness is not clear.

Conclusion

In this prospective study, low serum FT levels were associated with higher serum PSA, higher Gleason score and locally advanced or metastatic prostate cancer.

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